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Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 08 – 11 April 2019

Chair: Sabine Straus – Vice-Chair: Martin Huber

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scope listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review. Additional details on some of these procedures will be published in the [PRAC meeting highlights](#) once the procedures are finalised.

Of note, the minutes are a working document primarily designed for PRAC members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents ([EMA/127362/2006, Rev. 1](#)).



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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

The Chairperson opened the 08–11 April 2019 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex II - List of participants). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure ([EMA/PRAC/567515/2012 Rev.1](#)). All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chairperson announced that Ylva Böttiger resigned as the new alternate representing healthcare professionals and the position is vacant until a new nomination is granted from the European Commission (EC). In addition, the PRAC Chair announced that Daniela Philadelphia, the alternate for Austria, was to step down after the current plenary meeting. The PRAC highlighted her valuable contribution to the work of the Committee.

1.2. Agenda of the meeting on 08 – 11 April 2019

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat.

1.3. Minutes of the previous meeting on 11 – 14 March 2019

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 11–14 March 2019 were published on the EMA website on 3 July 2019 ([EMA/PRAC/235021/2019](#)).

2. EU referral procedures for safety reasons: urgent EU procedures

2.1. Newly triggered procedures

None

2.2. Ongoing procedures

None

2.3. Procedures for finalisation

None

3. EU referral procedures for safety reasons: other EU referral procedures

3.1. Newly triggered procedures

3.1.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/A-20/1483

Applicant: Sanofi Belgium

PRAC Rapporteur: Brigitte Keller-Stanislawski; PRAC Co-rapporteur: Ulla Wändel Liminga

Scope: Review of the benefit-risk balance following notification by European Commission of a referral under Article 20 of Regulation (EC) No 726/2004, based on pharmacovigilance data

Background

The European Commission (EC) sent a letter of [notification](#) dated 10 April 2019 triggering a procedure under Article 20 of Regulation (EC) No 726/2004 for the review of Lemtrada (alemtuzumab) a centrally authorised medicine, indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

During the assessment of the periodic safety update report single assessment (PSUSA) for Lemtrada (alemtuzumab) (PSUSA/00010055/201809), new emerging and serious safety concerns were brought to the attention of the PRAC in addition to the known safety profile of alemtuzumab. These safety concerns refer namely to fatal cases, cardiovascular adverse events in close temporal association with infusion of the medicinal product as well as immune-mediated diseases such as auto-immune hepatitis, hepatic injury, auto-immune-mediated central nervous system disease and Guillain-Barre syndrome. Limited information, including lack of detailed individual cases, was available on these concerns during the PSUSA assessment, which precluded a thorough evaluation. For further background, see under 6.1.1.

Therefore, the EC requested the EMA, following assessment, to give its opinion on whether the marketing authorisation(s) for Lemtrada (alemtuzumab) should be maintained, varied, suspended or revoked. In addition, the EC requested the EMA to give its opinion, as soon as possible, as to whether provisional measures were necessary to ensure the safe and effective use of the medicinal product.

Discussion

The PRAC noted the notification letter from the EC and appointed Brigitte Keller-Stanislawski as Rapporteur and Ulla Wändel Liminga as Co-Rapporteur for the procedure.

The PRAC reviewed the available data on cardiovascular and immune-mediated adverse events, including data provided by the MAH in the context of the PSUSA procedure (PSUSA/00010055/201809), the need for provisional measures to protect public health as well as a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review. The PRAC also discussed the need for a public hearing.

As part of the available data, several cases with various cardiovascular reactions were identified, including pulmonary alveolar haemorrhage, myocardial infarction, and ischaemic and haemorrhagic stroke as well as arterial dissection. Many of these cases were life-threatening or fatal. Common to these cardiovascular reactions was a close temporal relationship to an alemtuzumab infusion, which is suggestive of a causal association.

The PRAC also reviewed the available data on immune-mediated adverse events, including data provided by the MAH in the context of the PSUSA procedure. New life-threatening and potentially fatal immune-mediated adverse reactions were identified, including haemophagocytic lymphohistocytosis and autoimmune hepatitis. The PRAC also noted that recent literature reports have highlighted B-cell mediated central nervous system (CNS) lesions with temporal onset of 6 months after infusion of alemtuzumab.

In addition, several fatal cases were identified both in the literature and in the EudraVigilance database. Information from some fatal cases indicates that current recommendations for monitoring may be insufficient.

The PRAC noted that although efficacy of alemtuzumab in RRMS patients is well established, these emerging and serious safety concerns can impact the benefit-risk balance of Lemtrada (alemtuzumab), and that until a thorough review is finalised, it would be appropriate as a provisional measure to limit the patients exposed to alemtuzumab. Therefore, in view of the seriousness of the events observed, the PRAC recommended provisional amendments to the product information to restrict use of alemtuzumab in new patients to adults with highly active RRMS despite a full and adequate course of treatment with at least two other disease modifying treatments, or to adults with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments (DMTs) are contraindicated or otherwise unsuitable.

Furthermore, the PRAC considered important that the risk minimisation measures (RMMs) recommended within the assessment of the PSUSA procedure are also implemented together with the provisional measures. The PRAC recommended as part of the PSUSA procedure the addition of warnings related to serious reactions temporally associated with alemtuzumab infusion including pulmonary alveolar haemorrhage, myocardial infarction, stroke (including ischaemic and haemorrhagic stroke), cervicocephalic (e.g. vertebral, carotid) arterial dissection. New warnings on autoimmune hepatitis, hepatic injury and haemophagocytic lymphohistocytosis are also added. Furthermore, the following new adverse reactions are added: pulmonary alveolar haemorrhage, haemophagocytic lymphohistocytosis, myocardial infarction, stroke (including ischemic and haemorrhagic stroke), cervicocephalic arterial dissection and neutropenia.

The Committee considered that the benefit-risk balance of Lemtrada (alemtuzumab) remains favourable subject to the agreed provisional amendments to the product information.

Finally, the PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review.

Summary of recommendation(s)/conclusions

- The Committee recommended the variation¹ to the terms of the marketing authorisation(s) for Lemtrada (alemtuzumab) as a provisional measure, without

¹ Update of SmPC sections 4.4 and 4.8 and of Annex II. The package leaflet is updated accordingly

prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004.

- The PRAC also agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.
- The PRAC supported the organisation of a Scientific Advisory Group on Neurology ([SAG-N](#)) meeting in the course of the review.
- The Committee adopted a LoQ to the MAH ([EMA/PRAC/218935/2019](#)) and a timetable for the procedure ([EMA/PRAC/218954/2019](#)).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure² ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can reconsider this at a later stage of the procedure as needed.

See EMA press release ([EMA/220110/2019](#)) entitled 'Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing'.

Post-meeting note: The PRAC assessment report on provisional measures ([EMA/249094/2019](#)) and [scientific conclusions](#) were published on the EMA website on 8 May 2019. On 29 April 2019, the European Commission also granted a Commission Decision on the provisional measures ([C\(2019\)3379 \(final\)](#)).

3.1.2. Estradiol³ (NAP) - EMEA/H/A-31/1482

Applicant(s): various

PRAC Rapporteur: Eva Jirsova; PRAC Co-rapporteur: Menno van der Elst

Scope: Review of the benefit-risk balance following notification by European Commission of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Background

The European Commission (EC) sent a letter of [notification](#) dated 4 April 2019 triggering a procedure under Article 31 of Directive 2001/83/EC for the review of medicinal products containing estradiol (0.01% w/w) for topical use indicated for the treatment of vaginal atrophy due to oestrogen deficiency in post-menopausal women.

A previous review for medicinal products containing 0.01 g estradiol per 100 g (0.01% w/w) was initiated further to data showing plasma levels of estradiol similar to those associated with the use of estradiol in systemic hormone replacement therapy (HRT). This raised concerns about the occurrence of undesirable effects known for systemic HRT, which include venous thromboembolism, stroke, breast and endometrial cancer.

In April 2014, the EMA completed this review on the risk of systemic absorption with medicinal products containing estradiol (0.01% w/w) for topical use and recommended measures to minimise it, including amendment of the indication, restriction of the duration of use to a maximum of 4 weeks, withdrawal of the pack size of 100 g and adaptation to a

² Rules of procedure on the organisation and conduct of public hearings at the PRAC

³ 0.01%, topical use only

lower pack size (25g) and amendment of product information based on systemic HRT products. However, in March 2019 the European Union (EU) Court of Justice partially annulled the conclusions of that review on procedural grounds. Although the Court of Justice did not question the scientific conclusions, the partial annulment led to the invalidation of some of the measures taken to minimise the risks. Therefore, the EC expressed concerns that safety risks for those medicinal products are no longer addressed adequately and that patients are put at risk. As a consequence, the EC considered necessary to review the data assessed in the previous referral procedure for medicinal products containing estradiol for topical use as well as any data that would have become available since 2014 including case reports and literature references. The EC considered that it is in the interest of the Union to refer the matter to EMA and requested that the PRAC gives a recommendation as to whether the marketing authorisation(s) for these medicinal products should be maintained, varied, suspended or revoked.

Discussion

The PRAC noted the notification letter from the EC.

The PRAC appointed Eva Jirsova as Rapporteur and Menno van der Elst as Co-Rapporteur for the procedure.

The PRAC discussed a list of questions (LoQ) to be addressed during the procedure together with a timetable for conducting the review.

Summary of recommendation(s)/conclusions

- The Committee adopted a LoQ to the MAHs for medicinal products containing estradiol (0.01% w/w) for topical use ([EMA/PRAC/214199/2019](#)) and a timetable for the procedure ([EMA/PRAC/214200/2019](#)).
- The PRAC also discussed the option to conduct a public hearing in the context of the current procedure according to the pre-defined criteria set out in the rules of procedure⁴ ([EMA/363479/2015](#)). It was agreed by the Committee that at this stage of the procedure, in light of the currently available data and the need to determine the appropriate approach to stakeholder engagement, a public hearing would not be appropriate. The PRAC can come back to reconsider this at a later stage of the procedure as needed.

See EMA press release ([EMA/215459/2019](#)) entitled 'New review of risks with high-strength estradiol-containing creams'.

3.2. Ongoing procedures

None

3.3. Procedures for finalisation

None

⁴ Rules of procedure on the organisation and conduct of public hearings at the PRAC

3.4. Re-examination procedures⁵

None

3.5. Others

None

4. Signals assessment and prioritisation⁶

4.1. New signals detected from EU spontaneous reporting systems

See Annex I 14.1.

4.2. New signals detected from other sources

See also Annex I 14.2.

4.2.1. Loperamide (NAP)

Applicant(s): various

PRAC Rapporteur: Adam Przybylkowski

Scope: Signal of Brugada syndrome in the context of abuse with loperamide

EPITT 19379 – New signal

Lead Member State(s): PL

Background

Loperamide is an antipropulsive substance which slows down the movement of the intestines. Loperamide is indicated for the treatment of acute diarrhoea and treatment of acute episodes of diarrhoea associated with irritable bowel syndrome (IBS).

During routine signal detection activities, a signal of Brugada syndrome in the context of abuse with loperamide was identified by Poland, based on five cases retrieved from EudraVigilance and five cases reported in scientific literature. Poland confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of Brugada syndrome in the context of abuse with loperamide and considered that there was a plausible association between loperamide overdose and unmasking of Brugada syndrome. Therefore, the PRAC considered that it warrants an update of the product information for loperamide-containing medicines.

The PRAC appointed Adam Przybylkowski as Rapporteur for the signal.

⁵ Re-examination of PRAC recommendation under Article 32 of Directive 2001/83/EC

⁶ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Summary of recommendation(s)

- The MAH Johnson & Johnson Consumer B.V for the originator loperamide-containing product should submit to the EMA, within 30 days, comments on the proposal to amend the product information as agreed by the PRAC.
- A 30-day timetable was recommended for the assessment of the responses leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Armodafinil⁷ (NAP), modafinil (NAP)

Applicant(s): various

PRAC Rapporteur: Martin Huber

Scope: Evaluation of data on foetal outcomes including congenital anomalies from a single observational study in the US

EPITT 19367 – Follow-up to February 2019

Background

For background information, see [PRAC minutes February 2019](#).

The MAH Teva replied to the request for information on the signal of foetal outcomes including congenital anomalies and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the available information, including the clinical data reported in the literature, data from a pregnancy registry and data from an embryotoxicology centre as well as the responses to the PRAC list of questions (LoQ) provided by Teva, the MAH of the originator modafinil-containing product.

The PRAC concurred that modafinil is suspected of causing congenital malformations and should not be used during pregnancy. Therefore, the PRAC agreed that the product information of all modafinil-containing products should be updated in line with the guideline on 'Risk assessment of medicinal products on human reproduction and lactation: from data to labelling' ([EMEA/CHMP/203927/2005](#)). The PRAC also agreed on updating the RMP for medicinal products with one in place to include 'teratogenicity' as an important potential risk and to revise the frequency of PSUR submission to allow the assessment of yearly pregnancy registry interim reports.

Summary of recommendation(s)

- The MAHs for modafinil-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information⁸ and to update the RMP for products with an RMP in place.
- Teva, the MAH of the originator modafinil-containing product should submit to the relevant NCAs of the Member States, within 60 days, a variation to update the product

⁷ Armodafinil is not authorised in the EU

⁸ Update of SmPC sections 4.5. The package leaflet is to be updated accordingly

information section on preclinical safety data, supported by a review of all relevant available data.

- Teva, the MAH of the originator modafinil-containing product should also agree with the NCAs of the Member States where modafinil-containing product(s) are marketed the appropriate way of communication according to key messages agreed by the PRAC.
- The frequency of PSUR submission should be revised from three-yearly to yearly to allow for timely assessment of yearly pregnancy registry interim reports.

For the full PRAC recommendation, see [EMA/PRAC/219985/2019](#) published on 06/05/2019 on the EMA website.

4.3.2. Direct-acting oral anticoagulants (DOACs): apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/SDA/033; dabigatran etexilate – PRADAXA (CAP) - EMEA/H/C/000829/SDA/049; edoxaban - LIXIANA (CAP) - EMEA/H/C/002629/SDA/011, ROTEAS (CAP); rivaroxaban – XARELTO (CAP) - EMEA/H/C/000944/SDA/047

Applicant(s): Bayer AG (Xarelto), Boehringer Ingelheim (Pradaxa), Bristol-Myers Squibb Pharma EEIG (Eliquis), Daiichi Sankyo Europe (Lixiana, Roteas)

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of recurrent thrombosis in patients with antiphospholipid syndrome

EPITT 19320 – Follow-up to November 2018

Background

For background information, see [PRAC minutes November 2018 \(29-31 October 2018\)](#).

The MAHs of Eliquis (apixaban), Pradaxa (dabigatran), Lixiana (edoxaban), Roteas (edoxaban) and Xarelto (rivaroxaban) replied to the request for information on the signal of recurrent thrombosis in patients with antiphospholipid syndrome and the responses were assessed by the Rapporteur.

Discussion

Having considered all the available evidence from the literature, clinical trials and case reports from the post-marketing setting as well as the replies from the MAHs of direct acting oral anticoagulants (DOACs), the PRAC agreed that the product information of Eliquis (apixaban), Pradaxa (dabigatran), Lixiana (edoxaban), Roteas (edoxaban) and Xarelto (rivaroxaban) should be updated to include a warning that the use of DOACs is not recommended in patients with antiphospholipid syndrome and with a history of thrombosis. Given the possible increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome, the PRAC agreed on the distribution of a direct healthcare professional communication (DHPC) together with a communication plan.

Summary of recommendation(s)

- The MAHs for Eliquis (apixaban), Pradaxa (dabigatran), Lixiana (edoxaban), Roteas (edoxaban) and Xarelto (rivaroxaban) should submit to EMA, within 60 days, a variation to update the product information⁹.
- The MAHs for Eliquis (apixaban), Pradaxa (dabigatran), Lixiana (edoxaban), Roteas (edoxaban) and Xarelto (rivaroxaban) should distribute a single DHPC according to the communication plan agreed by the PRAC.

For the full PRAC recommendation, see [EMA/PRAC/219985/2019](#) published on 06/05/2019 on the EMA website.

4.3.3. **Idelalisib – ZYDELIG (CAP) - EMEA/H/C/003843/SDA/017**

Applicant(s): Gilead Sciences Ireland UC

PRAC Rapporteur: Martin Huber

Scope: Signal of arthritis and arthralgia

EPITT 19312 – Follow-up to December 2018

Background

For background information, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

The MAH replied to the request for information on the signal of arthritis and arthralgia and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the evidence from the cumulative review provided by the MAH, including information from clinical trials, epidemiology studies, published literature and a disproportionality analysis and agreed that at present, there is insufficient evidence to support a causal association between idelalisib and arthritis or arthralgia. The PRAC agreed that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAH for Zydelyg (idelalisib) should continue to monitor these events as part of routine pharmacovigilance.

4.3.4. **Inactivated poliomyelitis vaccine¹⁰ (NAP)**

Applicant(s): various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Signal of case reports from outside the EU of immune thrombocytopenic purpura

EPITT 19336 – Follow-up to December 2018

Background

For background information, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

⁹ Update of SmPC sections 4.4 (for all DOAC-containing products) and 5.1 (for Xarelto (rivaroxaban) only). The package leaflet is to be updated accordingly

¹⁰ Including combination vaccines

The MAH Sanofi Pasteur for Imovax Polio (inactivated poliomyelitis vaccine) replied to the request for information on the signal of case reports from outside the EU of immune thrombocytopenic purpura and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from the cumulative review of immune thrombocytopenic purpura (ITP) and related conditions in association with inactivated poliomyelitis vaccine (IPV) provided by the MAH, the PRAC agreed that at present, the evidence is insufficient to support a causal association between ITP and IPV. Therefore, the PRAC agreed that no further regulatory action is warranted at this stage.

Summary of recommendation(s)

- The MAHs for inactivated poliomyelitis vaccines should continue to monitor these events as part of routine pharmacovigilance.

4.3.5. Ivacaftor – KALYDECO (CAP) - EMEA/H/C/002494/SDA/025; ivacaftor, tezacaftor – SYMKEVI (CAP) - EMEA/H/C/004682/SDA/004

Applicant(s): Vertex Pharmaceuticals (Europe) Ltd.

PRAC Rapporteur: Rhea Fitzgerald

Scope: Signal of increased blood creatine phosphokinase (CPK)

EPITT 19316 – Follow-up to December 2018

Background

For background information, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

The MAH for Symkevi (tezacaftor/ivacaftor) and Kalydeco (ivacaftor) replied to the request for information on the signal of increased blood creatine phosphokinase (CPK) and the responses were assessed by the Rapporteur.

Discussion

Having considered the available evidence from EudraVigilance and the literature, as well as the cumulative review provided by the MAH, the PRAC agreed that there is at the moment insufficient evidence of a causal relationship between ivacaftor or tezacaftor/ivacaftor and increased blood CPK but noted that the causality assessment was missing for the majority of cases from clinical trials. The PRAC agreed that in the next PSUR the MAH for Symkevi (tezacaftor/ivacaftor) should provide an updated cumulative review including the causality assessment of all cases of increased blood CPK in association with tezacaftor/ivacaftor, as well as a discussion on the need for amendments to the product information and/or RMP.

Summary of recommendation(s)

- The MAH should submit to EMA, in the next PSUR of Symkevi (tezacaftor/ivacaftor) (data lock point (DLP): 11/08/2019), a cumulative review of all cases, including the causality assessment of all case reports (serious and non-serious) of increased blood CPK together with a proposal for amending the product information, as appropriate.

4.3.6. Selective serotonin reuptake inhibitors (SSRI): citalopram (NAP); escitalopram (NAP)

Applicant(s): various

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Signal of drug interaction with fluconazole

EPITT 19327 – Follow-up to December 2018

Background

For background information, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

The MAH H. Lundbeck A/S replied to the request for information on the signal of drug interaction with fluconazole and the responses were assessed by the Rapporteur.

Discussion

The PRAC considered the evidence on the drug interaction between citalopram or escitalopram and fluconazole, including additional data provided by the MAH H. Lundbeck A/S and noted that the number of cases was low considering the large exposure to citalopram or escitalopram. Nevertheless, the PRAC agreed that since fluconazole is a potent inhibitor of CYP2C19¹¹ and a moderate inhibitor of CYP3A4¹² and both isozymes are involved in the metabolism of citalopram or escitalopram, an update of the product information of citalopram- and escitalopram-containing products was warranted.

Summary of recommendation(s)

- The MAHs for citalopram- and escitalopram-containing products should submit to the relevant National Competent Authorities (NCAs) of the Member States, within 60 days, a variation to update the product information¹³.

For the full PRAC recommendation, see [EMA/PRAC/219985/2019](#) published on 06/05/2019 on the EMA website.

4.3.7. Sorafenib – NEXAVAR (CAP) - EMEA/H/C/000690/SDA/039

Applicant(s): Bayer AG

PRAC Rapporteur: Annika Folin

Scope: Signal of acute generalised exanthematous pustulosis (AGEP)

EPITT 18109 – Follow-up to December 2018

Background

For background information, see [PRAC minutes December 2018 \(26-29 November 2018\)](#).

The MAH for Nexavar (sorafenib) replied to the request for information on the signal of acute generalised exanthematous pustulosis (AGEP) and the responses were assessed by the Rapporteur.

Discussion

¹¹ Cytochrome P450 2C19

¹² Cytochrome P450 3A4

¹³ Update of SmPC sections 4.5. The package leaflet is to be updated accordingly

Having considered the available evidence, including the cumulative review provided by the MAH, the PRAC agreed that there is at present insufficient evidence for a causal association between sorafenib and AGEF. Therefore, the PRAC agreed that no further regulatory action was warranted at this stage.

Summary of recommendation(s)

- The MAH for Nexavar (sorafenib) should continue to monitor these events as part of routine pharmacovigilance.

5. Risk management plans (RMPs)

5.1. Medicines in the pre-authorisation phase

The PRAC provided the CHMP with advice on the proposed RMPs for a number of products (identified by active substance below) that are under evaluation for initial marketing authorisation. Information on the PRAC advice will be available in the European Public Assessment Reports (EPARs) to be published at the end of the evaluation procedure.

Please refer to the CHMP pages for upcoming information (<http://www.ema.europa.eu/Committees>CHMP>Agendas, minutes and highlights>).

See also Annex I 15.1.

5.1.1. Dolutegravir, lamivudine - EMEA/H/C/004909

Scope: Treatment of human immunodeficiency virus type 1 (HIV-1)

5.1.2. Enasidenib - EMEA/H/C/004324, Orphan

Applicant: Celgene Europe BV

Scope: Treatment of acute myeloid leukaemia (AML)

5.1.3. Glucagon - EMEA/H/C/003848

Scope: Treatment of severe hypoglycaemia

5.1.4. Polatuzumab vedotin - EMEA/H/C/004870, Orphan

Applicant: Roche Registration GmbH

Scope (accelerated assessment): Treatment of mature B cell lymphomas

5.1.5. Selinexor - EMEA/H/C/005127, Orphan

Applicant: Karyopharm Europe GmbH

Scope (accelerated assessment): Treatment of patients with relapsed refractory multiple myeloma (RRMM)

5.1.6. Sodium oxybate - EMEA/H/C/004962

Scope: Treatment of medium to long-term maintenance of alcohol abstinence and treatment of mild to moderate alcohol withdrawal syndrome

5.1.7. Tagraxofusp - EMEA/H/C/005031, Orphan

Applicant: TMC Pharma (EU) Limited

Scope (accelerated assessment): Treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)

5.2. Medicines in the post-authorisation phase – PRAC-led procedures

See Annex I 15.2.

5.3. Medicines in the post-authorisation phase – CHMP-led procedures

See also Annex I 15.3.

5.3.1. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/II/0071

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Extension of indication for Stelara to include treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. As a consequence, the SmPC, package leaflet and RMP (version 15.0) are updated

Background

Ustekinumab is an immunoglobulin (Ig)G1κ monoclonal antibody, indicated, as Stelara, for the treatment of Crohn's disease, plaque psoriasis, paediatric plaque psoriasis, psoriatic arthritis (PsA) under certain conditions.

The CHMP is evaluating a type II variation for Stelara, a centrally authorised product containing ustekinumab, consisting of an extension of indication to include treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP for Stelara (ustekinumab) in the context of the variation procedure under evaluation by the CHMP could be considered acceptable provided that an update to RMP version 15.0 is submitted.
- The MAH is requested to propose a PASS to further characterise long-term safety in patients with ulcerative colitis. The MAH should comment how the proposed design of the PASS will address the limitations of the long-term extension study of trial

CNT01275UCO3001¹⁴. The safety objectives for this study should include the important potential risk of venous thromboembolism.

6. Periodic safety update reports (PSURs)

6.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

See also Annex I 16.1.

6.1.1. Alemtuzumab - LEMTRADA (CAP) - PSUSA/00010055/201809 (with RMP)

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Alemtuzumab is an immunoglobulin (Ig)G1 kappa antibody indicated, as Lemtrada, for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Lemtrada, a centrally authorised medicine containing alemtuzumab and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Lemtrada (alemtuzumab) remains unchanged but the product information should be updated to include a warning on serious reactions temporally associated with Lemtrada (alemtuzumab) infusion including pulmonary alveolar haemorrhage, myocardial infarction, stroke (including ischaemic and haemorrhagic stroke), cervicocephalic (e.g. vertebral, carotid) arterial dissection, to add a warning on haemophagocytic lymphohistiocytosis and on autoimmune hepatitis and hepatic injury, and to revise a warning on use of alemtuzumab in patients with thyroid disorders. In addition, the product information should be updated to include as undesirable effects, pulmonary alveolar haemorrhage, myocardial infarction, stroke (including ischaemic and haemorrhagic stroke), cervicocephalic (e.g. vertebral, carotid) arterial dissection with a frequency 'not known', haemophagocytic lymphohistiocytosis with a frequency 'rare' as well as neutropenia with a frequency 'very common'. Therefore, the current terms of the marketing authorisation(s) should be varied¹⁵.
- In the next PSUR, the MAH should provide a detailed review of medication errors. The MAH should provide a root cause analysis of why the papers by *Buonomo et al*¹⁶ and

¹⁴ A phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis

¹⁵ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

¹⁶ Buonomo AR et al., Risk of opportunistic infections in patients treated with alemtuzumab for multiple sclerosis. Expert Opin Drug Saf. 2018;17(7):709-717.

*Pariani et al*¹⁷ were not identified in the literature search. In addition, the MAH should provide cumulative reviews of cholecystitis and of pericarditis. Finally, the MAH should provide point estimates of mortality incidence rates in study OBS13434¹⁸ over time.

In view of the seriousness of emerging safety concerns, namely fatal cases, cardiovascular adverse events and immune-mediated diseases, the PRAC supported the conduct of an in-depth investigation of these risks and a review on their impact on the benefit-risk balance of the medicinal product.

As a consequence the European Commission (EC) initiated on 10 April 2019 a referral procedure under Article 20 of Regulation (EC) No 726/2004 and requested the EMA to assess the above safety concerns and their impact on the benefit-risk balance of Lemtrada (alemtuzumab) including the need for provisional measures to ensure the safe and effective use of this medicinal product. See also under 3.1.1.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.2. Avelumab - BAVENCIO (CAP) - PSUSA/00010635/201809

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1) indicated, as Bavencio, in monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bavencio, a centrally authorised medicine containing avelumab and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Bavencio (avelumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include pancreatitis as an undesirable effect with a frequency 'rare', and to include it within the warning on immune-related adverse drug reactions (ADRs). Therefore, the current terms of the marketing authorisation(s) should be varied¹⁹.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

¹⁷ Pariani N, et al., Alemtuzumab-Induced Thyroid Dysfunction Exhibits Distinctive Clinical and Immunological Features. J Clin Endocrinol Metab. 2018;103(8):3010-3018.

¹⁸ A prospective, multicentre, observational, PASS to evaluate the long term safety profile of Lemtrada (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis

¹⁹ Update of SmPC sections 4.2, 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.3. Denosumab²⁰ - PROLIA (CAP) - PSUSA/00000954/201809

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Denosumab is a human immunoglobulin G2 (IgG2) that targets and binds with high affinity and specificity to the receptor activator of nuclear factor kappa-B ligand (RANKL). It is indicated, as Prolia, for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Prolia, a centrally authorised medicine containing denosumab and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Prolia (denosumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning regarding fatal cases of hypocalcaemia and to add lichenoid drug eruptions and alopecia as undesirable effects with frequency 'uncommon' and 'common', respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²¹.
- In the next PSUR, the MAH should provide a detailed review regarding the natural course of osteoporosis including occurrence and characteristics of fractures and a comparative analysis of this expected fracture pattern. The MAH should summarise available evidence regarding Prolia (denosumab) and fractures occurring after treatment discontinuation, including potential rebound effects, based on a review of literature, data from clinical trials as well as observational studies and discuss possible mechanistic explanations. In addition, the MAH should present the available evidence and clinical guidelines on how patients who discontinue treatment with Prolia (denosumab) may be managed and monitored. Furthermore, the MAH should provide an in-depth discussion on how more data can be obtained and possible study designs in order to investigate further the optimal treatment duration and on how best to manage patients who discontinue treatment with Prolia (denosumab).

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.4. Dexamethasone²² - NEOFORDEX (CAP) - PSUSA/00010480/201809

Applicant: Laboratoires CTRS

²⁰ Indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer only

²¹ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²² Centrally authorised product indicated in symptomatic multiple myeloma only

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

Background

Dexamethasone is a synthetic glucocorticoid with high anti-inflammatory effects with low mineralocorticoid activity. It is indicated, as Neofordex, for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Neofordex, a centrally authorised medicine containing dexamethasone and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Neofordex (dexamethasone) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning on the risk of tumour lysis syndrome (TLS). Therefore, the current terms of the marketing authorisation(s) should be varied²³.
- In the next PSUR, the MAH should closely monitor cases of lipemia retinalis, epidural lipomatosis, lipid metabolism disorders (mainly elevated cholesterol, elevated triglycerides, hyperlipidemia) and posterior reversible encephalopathy syndrome (PRES). The MAH should discuss new cases of TLS as well as the need to update the product information section on 'undesirable effects'.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.5. Idebenone²⁴ - RAXONE (CAP) - PSUSA/00010412/201809

Applicant: Santhera Pharmaceuticals (Deutschland) GmbH

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

Background

Idebenone is a short-chain benzoquinone indicated, as Raxone, for the treatment of visual impairment in adolescent and adult patients with Leber's hereditary optic neuropathy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Raxone, a centrally authorised medicine containing idebenone and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Raxone (idebenone) in the approved indication(s) remains unchanged.

²³ Update of SmPC section 4.4. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁴ Centrally authorised product(s) only

- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a review including the number of events of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyl-transferase increased, blood bilirubin increased and hepatitis observed in clinical and post-authorisation safety studies. The total number of exposed patients in the respective studies and pooled data should also be provided. In addition, the MAH should propose relevant frequencies for the reactions in the MedDRA SMQ²⁵ 'hepatic disorders' to update the product information, as appropriate.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.6. Insulin aspart - FIASP (CAP); NOVOMIX (CAP); NOVORAPID (CAP) - PSUSA/00001749/201809

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Insulin aspart is a fast-acting insulin indicated, as Fiasp, NovoMix and NovoRapid, for the treatment of diabetes mellitus.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of Fiasp, NovoMix and NovoRapid, centrally authorised medicines containing insulin aspart and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Fiasp, NovoMix and NovoRapid (insulin aspart) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include anaphylactic reactions as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁶.
- In the next PSUR, the MAH should provide updated information regarding the signal of 'change of efficacy', as well as an updated review on adverse events related to leakage complaints and provide detailed information on reporting rates of events of product administration errors for NovoRapid (insulin aspart).

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

²⁵ Medical Dictionary for Regulatory Activities – Standardised MedDRA Queries

²⁶ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.7. Lacosamide - VIMPAT (CAP) - PSUSA/00001816/201808

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Lacosamide is an anti-epileptic indicated, as Vimpat, in monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vimpat, a centrally authorised medicine containing lacosamide and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Vimpat (lacosamide) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a root cause analysis regarding reasons for chopping of tablets, following post-marketing reports of a possible association between chopping of lacosamide tablets and the occurrence of seizure, lack of efficacy or other adverse events. The MAH should include a discussion on other actions to minimise this risk beyond updates of product information. The MAH should also provide a cumulative review on metabolic/toxic encephalopathy.
- In the next PSUR, the MAH should present a cumulative review exposure in pregnancy, a cumulative review on breastfeeding cases and make proposals to update the product information, as appropriate.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.8. Naloxegol - MOVENTIG (CAP) - PSUSA/00010317/201809

Applicant: Kyowa Kirin Holdings B.V.

PRAC Rapporteur: Ronan Grimes

Scope: Evaluation of a PSUSA procedure

Background

Naloxegol is a PEGylated²⁷ derivative of naloxone and is indicated, as Moventig, for the treatment of opioid-induced constipation in adult patients who have had an inadequate response to laxative(s).

²⁷ Polyethylene glycol

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Moventig, a centrally authorised medicine containing naloxegol and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Moventig (naloxegol) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to refine the existing warning on gastrointestinal perforation and add gastrointestinal perforation as an undesirable effect with a frequency 'not known'. Therefore, the current terms of the marketing authorisation(s) should be varied²⁸.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.9. Naltrexone, bupropion - MYSIMBA (CAP) - PSUSA/00010366/201809

Applicant: Orexigen Therapeutics Ireland Limited

PRAC Rapporteur: Martin Huber

Scope: Evaluation of a PSUSA procedure

Background

Naltrexone is a mu-opioid antagonist and bupropion is a weak inhibitor of neuronal dopamine and norepinephrine reuptake. In combination, naltrexone/bupropion is indicated, as Mysimba, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients with an initial body mass index (BMI) of 30 kg/m² or greater (obese), or between 27 kg/m² and 30 kg/m² (overweight) in the presence of one or more weight-related co-morbidities (e.g. type 2 diabetes mellitus, dyslipidaemia or controlled hypertension).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Mysimba, a centrally authorised medicine containing naltrexone/bupropion and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Mysimba (naltrexone/bupropion) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a warning that naltrexone/bupropion may affect the ability to drive or to use machines and to add somnolence and loss of consciousness as undesirable effects with a frequency 'common' and 'rare' respectively. Therefore, the current terms of the marketing authorisation(s) should be varied²⁹.

²⁸ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

²⁹ Update of SmPC sections 4.4, 4.7 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should provide a detailed evaluation of tolerability issues related to naltrexone/bupropion including a discussion on cases in which patients intentionally reduced the dose or stopped taking naltrexone/bupropion due to tolerability issues as well as of patients who continued therapy despite tolerability issues. In addition, the MAH should closely monitor potential interactions of naltrexone/bupropion with warfarin and propofol and provide a review of reported cases and published literature. Furthermore, the MAH should provide a cumulative review of panic-related case reports as well as a review of the relevant literature, and discuss whether an update of the product information or other risk minimisation measures are warranted. Finally, the MAH should provide a detailed discussion on the non-interventional study entitled: 'Mysimba in real clinical practice and its effect on body weight reduction'.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.10. Niraparib - ZEJULA (CAP) - PSUSA/00010655/201809

Applicant: Tesaro Bio Netherlands B.V.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

Background

Niraparib is an inhibitor of poly (adenosine diphosphate (ADP)-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2. It is indicated, as Zejula, for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Zejula, a centrally authorised medicine containing niraparib and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Zejula (niraparib) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include febrile neutropenia as an undesirable effect with a frequency 'uncommon'. Therefore, the current terms of the marketing authorisation(s) should be varied³⁰.
- In the next PSUR, the MAH should discuss the publications by *Alecu et al*³¹ and *Liu et al*³² in view of potential haematologic and gastrointestinal toxicities respectively. In addition, the MAH should discuss the risk of thromboembolic events in patients with pre-

³⁰ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³¹ Alecu I, Milenkova T and Turner SR. Risk of severe hematologic toxicities in cancer patients treated with poly ADP ribose polymerase (PARP). PARP inhibitors: results of monotherapy and combination therapy trials. Drug Des Devel Ther. 2018; 12: 347–348

³² Liu Y, Meng J and Wang G. Risk of selected gastrointestinal toxicities associated with poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors in the treatment of ovarian cancer: a meta-analysis of published trials. Drug Des Devel Ther. 2018; 12: 3013–3019

existing cardiac disorders with a view to updating the product information as warranted, considering the warning on monitoring of patients with cardiac insufficiency and cardiac arrhythmias included in the US prescribing information. The MAH is requested to monitor the effects of the posology change on the reported incidence of grade 3/4 thrombocytopenia should changes in posology be introduced.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.11. Ocrelizumab - OCREVUS (CAP) - PSUSA/00010662/201809

Applicant: Roche Registration GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

Background

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B cells. It is indicated, as Ocrevus, for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features and for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Ocrevus, a centrally authorised medicine containing ocrelizumab and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Ocrevus (ocrelizumab) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include additional information with regards to an association between low immunoglobulin level and risk of serious infections. Therefore, the current terms of the marketing authorisation(s) should be varied³³.
- In the next PSUR, the MAH should perform a cumulative review of cases of sepsis (including urosepsis) from clinical studies and post-marketing surveillance, review cases of serious infections reported with ocrelizumab therapy in multiple sclerosis indication to further characterize the risk and to assess whether any updates of the product information and/or RMP are warranted, and to discuss the effect of ocrelizumab on T-cell subgroups. In addition, the MAH should comment on hepatitis B reactivation following ocrelizumab treatment, considering reports from spontaneous sources and literature. The MAH should also provide a cumulative review of all fatal cases as well as an analysis of incidence of all malignancies by tumour type from clinical studies and other sources, including Kaplan-Meier analyses.

³³ Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.12. Rivaroxaban - XARELTO (CAP) - PSUSA/00002653/201809

Applicant: Bayer AG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Rivaroxaban is a factor Xa inhibitor indicated, as Xarelto, with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers and co-administered with ASA, for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. It is also indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery, for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), for the prevention of recurrent DVT and PE in adults, and for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Xarelto, a centrally authorised medicine containing rivaroxaban and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Xarelto (rivaroxaban) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to delete a footnote relating to the undesirable effect renal impairment (incl. blood creatinine increased, blood urea increased) on the 'prevention of VTE in adult patients undergoing elective hip or knee replacement surgery'. In addition, the instructions on how to take Xarelto (rivaroxaban) in the package leaflet should be updated. Therefore, the current terms of the marketing authorisation(s) should be varied³⁴.
- In the next PSUR, the MAH should present cases of pancreatitis with a temporal relationship and positive dechallenge/rechallenge. The MAH should also present a review of cases of ulcerative colitis with close temporal relationship, positive de- or re-challenge, and not related to bleeding. In addition, the MAH should provide a cumulative review of the interaction between grapefruit juice and rivaroxaban and discuss the need for an update of the product information as warranted.

³⁴ Update of SmPC section 4.8 and package leaflet section 3. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.13. Trabectedin - YONDELIS (CAP) - PSUSA/00003001/201809

Applicant: Pharma Mar, S.A.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

Background

Trabectedin is an anti-neoplastic agent, indicated as Yondelis, for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents, and in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum-sensitive ovarian cancer.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Yondelis, a centrally authorised medicine containing trabectedin and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Product (trabectedin) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a thorough presentation and background for the performed cardiac safety analyses, including further information on the methods, models and variables selected as risk factors and clarifications for the obtained results.
- In the next PSUR, the MAH should comment on the findings by *Vincenzi et al*³⁵, suggesting that body mass index was significantly associated with increased frequency and severity of neutropenia in patients with soft tissue sarcoma, including a discussion on the need to update the product information as warranted.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.14. Trientine - CUPRIOR (CAP) - PSUSA/00010637/201809

Applicant: GMP-Orphan SA

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

Background

³⁵ Vincenzi B et al. Body mass index as a risk factor for toxicities in patients with advanced soft-tissue sarcoma treated with trabectedin. *oncology*. 2018;95(1):1-7

Trientine is a copper-chelating agent indicated, as Cuprior, for the treatment of Wilson's disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Cuprior, a centrally authorised medicine containing trientine and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Cuprior (trientine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include a description of the symptoms and signs observed in cases of overdose. Therefore, the current terms of the marketing authorisation(s) should be varied³⁶.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.15. Vortioxetine - BRINTELLIX (CAP) - PSUSA/00010052/201809

Applicant: H. Lundbeck A/S

PRAC Rapporteur: Laurence de Fays

Scope: Evaluation of a PSUSA procedure

Background

Vortioxetine is a 5-hydroxytryptamine (5-HT): 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, a 5-HT_{1A} receptor agonist and a 5-HT transporter inhibitor. It is indicated, as Brintellix, for the treatment of major depressive episodes in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Brintellix, a centrally authorised medicine containing vortioxetine and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Brintellix (vortioxetine) in the approved indication(s) remains unchanged.
- Nevertheless, the product information should be updated to include anaphylactic reaction, haemorrhage (including contusion, ecchymosis, epistaxis, gastrointestinal or vaginal bleeding) and rash as undesirable effects with a frequency 'not known'. Additionally, the class warning on haemorrhage should be updated, to add that haemorrhage has also been reported with vortioxetine. Therefore, the current terms of the marketing authorisation(s) should be varied³⁷.

³⁶ Update of SmPC section 4.9. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

³⁷ Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

- In the next PSUR, the MAH should provide a detailed review of medication errors. The MAH should also discuss the article by *Subeesh et al*³⁸ and provide detailed cumulative reviews of cases of weight loss, agitation, anger, aggression, ketoacidosis, convulsions/seizures, pancreatitis and insomnia, including a discussion on the need for updating the product information as warranted. The MAH should also present a detailed analysis of clinical trial and post-marketing data on suicidal ideation and behaviour.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.16. Zoledronic acid³⁹ - ACLASTA (CAP) - PSUSA/00009334/201808

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

Background

Zoledronic acid is a nitrogen-containing bisphosphonate indicated, as Aclasta, for the treatment of osteoporosis in post-menopausal women and adult men at increased risk of fracture and treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and adult men at increased risk of fracture, and for the treatment of Paget's disease of the bone in adults.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Aclasta, a centrally authorised medicine containing zoledronic acid and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of Aclasta (zoledronic acid) in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA, within 60 days, a structured review regarding rheumatological/immune-mediated syndrome (RIMS) following intravenous bisphosphonate therapy from pooled controlled clinical studies. The MAH should present the data separately for each of the phase 3 studies (placebo-controlled studies) as well as pooled data. Cases of RIMS and acute phase reactions should be presented as numbers per patients and also per given injections. Finally, the MAH should present a non-clinical review and a review of post-marketing cases.

The frequency of PSUR submission should be revised from three-yearly to five-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

³⁸ Subeesh V et al. Novel adverse events of vortioxetine: A disproportionality analysis in US FDA adverse event reporting system database. *Asian J Psychiatr.* 2017;30:152-156

³⁹ Indicated for osteoporosis only

6.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

See Annex I 16.2.

6.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

See also Annex I 16.3.

6.3.1. Finasteride (NAP) - PSUSA/00001392/201808

Applicant(s): various

PRAC Lead: Annika Folin

Scope: Evaluation of a PSUSA procedure

Background

Finasteride is an inhibitor of type II 5 alpha reductase indicated, in the 5 mg strength, for the treatment of treatment of benign prostatic hyperplasia and for prevention of urologic events to reduce the risk of acute urinary retention as well as to reduce the risk of surgery. It is also indicated, in the 1 mg strength, for the treatment of male pattern hair loss.

Based on the assessment of the PSUR(s), the PRAC reviewed the benefit-risk balance of nationally authorised medicine(s) containing finasteride and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the benefit-risk balance of finasteride-containing medicinal products in the approved indication(s) remains unchanged.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, MAHs should closely monitor the persistence of psychiatric events after discontinuation of finasteride together with a discussion on biological plausibility of these events and possible risk factors for persistence of these events. In addition, the MAHs should closely monitor cases of suicide and self-injury taking into account medical history and concurrent medical condition and risk factors, muscle-related events and rhabdomyolysis. Finally, the MAHs should conduct a thorough literature search⁴⁰ and present a discussion of the findings.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The requirement to submit PSUR(s) for products referred to in Articles 10(1),

⁴⁰Including and not limited to: Lee et al. Adverse sexual effects of treatment with finasteride or dutasteride for male androgenetic alopecia: a systematic review and meta-analysis. *Acta Dermato-Venereologica*. 2019; 99: 12-17
Baas et al. A Review of the FEARS data on 5-alpha reductase inhibitors: implication for post finasteride syndrome. *Urology*. 2018; 120:143-149
Fertig et al. Sexual side effects of 5-α-reductase inhibitors finasteride and dutasteride: a comprehensive review. *Dermatol Online J*. 2017; 23(11)

10a, 16a of Directive 2001/83/EC does not apply any longer. The EURD list is updated accordingly.

6.4. Follow-up to PSUR/PSUSA procedures

See also Annex I 16.4.

6.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 034

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Detailed review of cases of alopecia in patients using apixaban from post marketing cases, clinical trial data, and literature including cases with a possible or probable relationship due to missing information, as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00000226/201805 adopted at the December 2018 PRAC meeting (held on 26-29 November 2018)

Background

Apixaban is a factor Xa inhibitor, direct oral anticoagulant (DOAC) indicated, as Eliquis, for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (NVAf), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA15 class $\geq$ II). It is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data. For further background, see [PRAC minutes December 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and concluded that there is sufficient evidence to support a causal association between apixaban and alopecia. Therefore, the PRAC agreed that the MAH should submit to the EMA, within 60 days, a variation to update the product information to include alopecia as an undesirable effect with a frequency 'rare' (for the VTE prevention indication) or 'uncommon' (for the NVAf and VTE treatment indications).

6.4.2. Clopidogrel - CLOPIDOGREL ZENTIVA (CAP) - EMEA/H/C/000975/LEG 014

Applicant: Zentiva k.s.

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Review of the risk of interaction between morphine and clopidogrel as agent of the class of P2Y₁₂ inhibitors, as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00002499/201802 for prasugrel adopted in September 2018

Background

Clopidogrel is an inhibitor of platelet aggregation indicated, as Clopidogrel Zentiva, for the secondary prevention of atherothrombotic events in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease, adult patients suffering from acute coronary syndrome and for the prevention of atherothrombotic and thromboembolic events in adult patient with atrial fibrillation subject to certain conditions.

Following the evaluation of the most recently submitted PSURs for prasugrel, a medicine of the same therapeutic class, the PRAC requested the MAH to submit further data. For further background, see [PRAC minutes September 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and concluded that there is sufficient evidence on the interaction between clopidogrel and morphine when co-administered, resulting in reduced clopidogrel efficacy. Therefore, the PRAC agreed that the MAH should submit to the EMA, within 60 days, a variation to update the product information to include a warning on this interaction in the product information section on 'interaction with other medicinal products and other forms of interaction'.

6.4.3. Clopidogrel - ISCOVER (CAP) - EMEA/H/C/000175/LEG 032

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Review of the risk of interaction between morphine and clopidogrel as agent of the class of P2Y₁₂ inhibitors, as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00002499/201802 for prasugrel adopted in September 2018

Background

Clopidogrel is an inhibitor of platelet aggregation indicated, as Iscover, for the secondary prevention of atherothrombotic events in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease, adult patients suffering from acute coronary syndrome and for the prevention of atherothrombotic and thromboembolic events in adult patient with atrial fibrillation subject to certain conditions.

Following the evaluation of the most recently submitted PSURs for prasugrel, a medicine of the same therapeutic class, the PRAC requested the MAH to submit further data. For further background, see [PRAC minutes September 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and concluded that there is sufficient evidence on the interaction between clopidogrel and morphine when co-administered, resulting in reduced clopidogrel efficacy. Therefore, the PRAC agreed that the MAH should submit to the EMA, within 60 days, a variation to update the product information to include a warning on this interaction in the product information section on 'interaction with other medicinal products and other forms of interaction'.

6.4.4. Clopidogrel - PLAVIX (CAP) - EMEA/H/C/000174/LEG 035

Applicant: Sanofi Clir SNC

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Review of the risk of interaction between morphine and clopidogrel as agent of the class of P2Y₁₂ inhibitors, as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00002499/201802 for prasugrel adopted in September 2018

Background

Clopidogrel is an inhibitor of platelet aggregation indicated, as Plavix, for the secondary prevention of atherothrombotic events in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease, adult patients suffering from acute coronary syndrome and for the prevention of atherothrombotic and thromboembolic events in adult patient with atrial fibrillation subject to certain conditions.

Following the evaluation of the most recently submitted PSURs for prasugrel, a medicine of the same therapeutic class, the PRAC requested the MAH to submit further data. For further background, see [PRAC minutes September 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and concluded that there is sufficient evidence on the interaction between clopidogrel and morphine when co-administered, resulting in reduced clopidogrel efficacy. Therefore, the PRAC agreed that the MAH should submit to the EMA, within 60 days, a variation to update the product information to include a warning on this interaction in the product information section on 'interaction with other medicinal products and other forms of interaction'.

6.4.5. Clopidogrel, acetylsalicylic acid - CLOPIDOGREL/ACETYLSALICYLIC ACID ZENTIVA (CAP) - EMEA/H/C/001144/LEG 010

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Review of the risk of interaction between morphine and clopidogrel as agent of the class of P2Y₁₂ inhibitors, as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00002499/201802 for prasugrel adopted in September 2018

Background

Clopidogrel is an inhibitor of platelet aggregation and acetylsalicylic acid is an analgesic, antipyretic and anti-inflammatory medicine with antithrombotic action which is mediated through inhibition of platelet activation, indicated, as Clopidogrel/acetylsalicylic acid Zentiva, for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid for continuation of therapy in non-ST segment elevation acute coronary syndrome and ST segment elevation acute myocardial infarction subject to certain conditions.

Following the evaluation of the most recently submitted PSURs for prasugrel, a medicine of the same therapeutic class, the PRAC requested the MAH to submit further data. For further background, see [PRAC minutes September 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and concluded that there is sufficient evidence on the interaction between clopidogrel and morphine when co-administered, resulting in reduced clopidogrel efficacy. Therefore, the PRAC agreed that the MAH should submit to the EMA, within 60 days, a variation to update the product information to include a warning on this interaction in the product information section on 'interaction with other medicinal products and other forms of interaction'.

6.4.6. Clopidogrel, acetylsalicylic acid - DUOPLAVIN (CAP) - EMEA/H/C/001143/LEG 013

Applicant: Sanofi Clir SNC

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Review of the risk of interaction between morphine and clopidogrel as agent of the class of P2Y₁₂ inhibitors, as requested in the conclusions of periodic safety update single assessment procedure PSUSA/00002499/201802 for prasugrel adopted in September 2018

Background

Clopidogrel is an inhibitor of platelet aggregation and acetylsalicylic acid is an analgesic, antipyretic and anti-inflammatory medicine with antithrombotic action which is mediated through inhibition of platelet activation, indicated, as DuoPlavin, for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid for continuation of therapy in non-ST segment elevation acute coronary syndrome and ST segment elevation acute myocardial infarction subject to certain conditions.

Following the evaluation of the most recently submitted PSURs for prasugrel, a medicine of the same therapeutic class, the PRAC requested the MAH to submit further data. For further background, see [PRAC minutes September 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and concluded that there is sufficient evidence on the interaction between clopidogrel and morphine when co-administered, resulting in reduced clopidogrel efficacy. Therefore, the PRAC agreed that the MAH should submit to the EMA, within 60 days, a variation to update the product information to include a warning on this interaction in the product information section on 'interaction with other medicinal products and other forms of interaction'.

6.4.7. Interferon beta-1a - REBIF (CAP) - EMEA/H/C/000136/LEG 044

Applicant: Merck Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Detailed justification regarding the decrease of spontaneous reports during the period covered by the PSUSA procedure together with a cumulative review of cases of panniculitis, as requested in the conclusions of periodic single assessment procedure PSUSA/00009198/201805 adopted at the December 2018 PRAC (held on 26-29 November 2018)

Background

Interferon beta-1a is a recombinant interferon, a glycoprotein endowed with immunomodulatory, antiviral and antiproliferative properties. It is indicated, as Rebif, for the treatment of patients diagnosed with relapsing multiple sclerosis (MS).

Following the evaluation of the most recently submitted PSUR(s) for the above mentioned medicine(s), the PRAC requested the MAH of Rebif (interferon beta-1a) to submit further data. For further background, see [PRAC minutes December 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and considered that the MAH's responses regarding the decrease of spontaneous reports during the period covered by the PSUSA procedure were acceptable. Based on the cumulative review of postmarketing safety data on panniculitis including cases with a biopsy-confirmed diagnosis, positive dechallenge and reasonable time to onset, the PRAC also concluded that panniculitis can occur at the injection site in patients treated with Rebif (interferon beta-1a). Therefore, the PRAC agreed that the MAH should submit to EMA, within 60 days, a variation to update the product information to include injection site panniculitis as an undesirable effect with a frequency 'not known'.

6.4.8. Pixantrone - PIXUVRI (CAP) - EMEA/H/C/002055/LEG 012

Applicant: CTI Life Sciences Deutschland GmbH

PRAC Rapporteur: Kimmo Jaakkola

Scope: Detailed review for all phase 3 trials including study PIX306⁴¹ as well as for study PIXreal⁴² of the number and proportion of patients for each study with information on possible dose lowering and/or dose omission/skipping, as requested in the conclusions of periodic single assessment procedure PSUSA/00009261/201805 adopted at the December 2018 PRAC (held on 26-29 November 2018)

Background

Pixantrone is a cytotoxic aza-anthracenedione indicated, as Pixuvri, for the treatment in monotherapy of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell Lymphomas (NHL).

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data. For further background, see [PRAC minutes December 2018](#). The responses were assessed by the Rapporteur for further PRAC advice.

Summary of advice/conclusion(s)

- The PRAC supported the Rapporteur's assessment and agreed that the available data are inconclusive concerning dose modifications in the real-world use. Therefore, the

⁴¹ A randomised multicentre study comparing pixantrone + rituximab with gemcitabine + rituximab in patients with aggressive B-cell non-Hodgkin lymphoma who have relapsed after therapy with CHOP-R (cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone - rituximab) or an equivalent regimen and are ineligible for stem cell transplant

⁴² An observational, multicentre, open label study of pixantrone 50mg/m² given on days 1, 8, and 15 of each 28 day cycle for up to 6 cycles for the treatment of adult patients with multiple relapsed or refractory aggressive B cell non-Hodgkin lymphomas

PRAC concurred that no changes were warranted to the dose modification guidance of the product information.

7. Post-authorisation safety studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)⁴³

See also Annex I 7.1.

7.1.1. Tolvaptan - JINARC (CAP) - EMEA/H/C/PSA/S/0031.1

Applicant: Otsuka Pharmaceutical Europe Ltd

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to PSA/S/0031 [amendment to a protocol initially endorsed by PRAC in March 2016 (PSP/0028.2) for a 4-year, multicentre, non-interventional PASS to measure the effectiveness of the risk minimisation measures in reducing the severity of liver injury in patients who experience an elevation of transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) > 3× upper limit of normal (ULN), or an adverse event (AE) consistent with hepatotoxicity in real life] as per the request for supplementary information (RSI) adopted in October 2018

Background

Tolvaptan is a vasopressin antagonist indicated, as Jinarc a centrally authorised medicine, to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product ([Annex II-D of the marketing authorisation\(s\)](#)) a non-interventional PASS has to be conducted to investigate the risks of hepatotoxicity, basal cell carcinoma, glaucoma associated with the use of Jinarc (tolvaptan). In addition, the study should also provide information on pregnancy outcomes, patterns of medicinal product utilisation, especially with regards to off-label use and use in patients over 50 years old, and adverse drug reactions associated with long term use. In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted a PASS protocol for study 156-12-299 that was endorsed by PRAC in March 2016 (procedure PSP/0028.2). In January 2019, the MAH submitted substantial amendments in accordance with Article 107o of Directive 2001/83/EC to the previously agreed non-interventional imposed PASS protocol. Amended PASS protocols B and C version 3 for study 156-12-299 entitled 'a 9-year, multicentre, non-interventional, post-authorisation safety study for patients prescribed Jinarc (tolvaptan) for autosomal dominant polycystic kidney disease' is assessed within the procedure. The PRAC is responsible for evaluating the PASS protocol. For further background, see [PRAC minutes March 2016](#) and [PRAC minutes October 2018](#).

Endorsement/Refusal of the protocol

⁴³ In accordance with Article 107n of Directive 2001/83/EC

- The PRAC, having considered the amended PASS protocols B and C version 3 in accordance with Article 107o of Directive 2001/83/EC, endorsed the protocol for study 156-12-299 for Jinarc (tolvaptan).
- The MAH should submit a variation to the EMA to update the RMP and Annex II accordingly.

7.1.2. Voretigene neparvovec - LUXTURNA (CAP) - EMEA/H/C/PSP/S/0078

Applicant: Novartis Europharm Ltd, ATMP⁴⁴

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Protocol for a post-authorisation observational study to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products

Background

Voretigene neparvovec is an adeno-associated virus vector-based gene therapy substance indicated, as Luxturna, for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic retinal pigment epithelium-specific 65 kilodalton (kDa) protein (RPE65) mutations and who have sufficient viable retinal cells.

As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product ([Annex II-D of the marketing authorisation\(s\)](#)) a non-interventional PASS has to be conducted to further characterise the safety and long-term safety of Luxturna (voretigene neparvovec) based on data from a disease registry in patients vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations (SPKRPE-EUPASS). In order to fulfil the obligation to conduct a PASS imposed in accordance with Article 107n(3) of Directive 2001/83/EC, the MAH submitted PASS protocol version 00 for study CLTW888A12401 entitled 'a post-authorisation, multicentre, multinational, longitudinal, observational safety registry study for patients treated with voretigene neparvovec'. The PRAC is responsible for evaluating the PASS protocol.

Endorsement/Refusal of the protocol

- The PRAC, having reviewed PASS protocol version 00 and in accordance with Article 107n of Directive 2001/83/EC, considered that the PASS is non-interventional but the study design does not fulfil the study objectives at this stage as several minor objections remain to be resolved before the protocol can be considered adequate. The protocol for Luxturna (voretigene neparvovec) PASS could be acceptable provided that satisfactory responses are provided regarding in particular the limited retrospective inclusion of patients. In addition, the MAH should confirm that annual follow-ups will be performed preferably in the 'Luxturna treatment centres' and inherited retinal dystrophy referral centres. The MAH should also include a follow-up period of newborns for events not evident at birth. Furthermore, the MAH should also provide a comparison of baseline incidences of adverse event of special interest (AESIs) and (serious) adverse events ((S)AEs) known for the disease.

⁴⁴ Advanced therapy medicinal product

- The MAH should submit a revised PASS protocol within 30 days to the EMA. A 60 day-assessment timetable will be followed.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁴⁵

See Annex I 17.2.

None

7.3. Results of PASS imposed in the marketing authorisation(s)⁴⁶

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)⁴⁷

See also Annex I 17.4.

7.4.1. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/II/0085

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study CNTO148ART4002 (listed as a category 3 study in the RMP): an observational phase 4 study using the Optum Research Database (ORD) to estimate the long-term safety profile in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) who are initiating Simponi (golimumab) treatment and/or other types of biologic and non-biologic treatments. The RMP (version 19.0) is updated accordingly and in line with revision 2 of GVP module V on 'Risk management systems' in order to reflect changes in the categorisation of safety concerns

Background

Golimumab is a tumour necrosis factor alfa (TNF- α) inhibitor indicated, as Simponi a centrally authorised medicine, for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis (pJIA), psoriatic arthritis (PsA), axial spondyloarthritis, ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-Axial SpA) and ulcerative colitis (UC) under certain conditions.

As stated in the RMP of Simponi (golimumab), the MAH conducted a non-imposed non-interventional study CNTO148ART4002 using the Optum Research Database (ORD), a large United States (US) health insurance claim database, to estimate the long-term safety profile in patients with RA, PsA, and AS who are initiating Simponi treatment and/or other types of biologic and non-biologic treatments. The Rapporteur assessed the MAH's final study report. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation. For further background, see [PRAC minutes January 2019](#).

⁴⁵ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

⁴⁶ In accordance with Article 107p-q of Directive 2001/83/EC

⁴⁷ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

Summary of advice

- Based on the available data, the MAH's answers to the request for supplementary information (RSI) and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report could be considered acceptable provided that satisfactory responses to a further RSI are submitted.
- The MAH should provide a further in-depth justification for removing congestive heart failure (CHF) from the patient reminder card and the summary of safety concerns. Other changes to the patient reminder card should also be justified. In addition, the MAH should add to the patient card information on breakthrough infections after administration of live vaccines in infants exposed to golimumab in utero.

7.4.2. Infiximab - REMICADE (CAP) - EMEA/H/C/000240/II/0218

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final study report from the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) cohort 2 portion of the registry: a German rheumatoid arthritis (RA) registry established as a prospective observational cohort study on the long-term safety and effectiveness of biologic disease-modifying anti-rheumatic drugs (DMARDs) in patients with RA. The RMP (version 19) is updated accordingly. The MAH also revised the RMP list of safety concerns as requested in the conclusions of procedure LEG 156 adopted in October 2017

Background

Infiximab is a tumour necrosis factor alfa (TNF- α) inhibitor indicated, as Remicade a centrally authorised medicine, for the treatment of rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis under certain conditions.

As stated in the RMP of Remicade (infiximab), the MAH conducted a non-imposed non-interventional PASS entitled 'Rheumatoide Arthritis - Beobachtung der Biologika-Therapie (RABBIT) German RA registry cohort 2' established as a prospective observational cohort study on the long-term safety and effectiveness of biologic disease-modifying anti-rheumatic drugs in patients with RA. The Rapporteur assessed the MAH's final study report. The PRAC is responsible for producing an assessment report to be further considered at the level of the CHMP, which is responsible for adopting an opinion on this variation. For further background, see [PRAC minutes January 2019](#).

Summary of advice

- Based on the available data, the MAH's answers to the request for supplementary information (RSI) and the Rapporteur's review, the PRAC considered that the ongoing variation assessing the final study report could be considered acceptable provided that satisfactory responses to a further RSI are submitted.
- The MAH should provide a further in-depth justification for removing congestive heart failure (CHF) from the patient reminder card and the summary of safety concerns. Other changes to the patient reminder card should also be justified.

7.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation

See Annex I 17.5.

7.6. Others

See Annex I 17.6.

7.7. New Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

7.8. Ongoing Scientific Advice

None

7.9. Final Scientific Advice (Reports and Scientific Advice letters)

None

8. Renewals of the marketing authorisation, conditional renewal and annual reassessments

8.1. Annual reassessments of the marketing authorisation

See Annex I 18.1.

8.2. Conditional renewals of the marketing authorisation

See Annex I 18.2.

8.3. Renewals of the marketing authorisation

See also Annex I 18.3.

8.3.1. Fentanyl - INSTANYL (CAP) - EMEA/H/C/000959/R/0049 (with RMP)

Applicant: Takeda Pharma A/S

PRAC Rapporteur: Ghania Chamouni

Scope: 5-year renewal of the marketing authorisation

Background

Fentanyl is an opioid analgesic indicated, as Instanyl, for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

Instanyl, a centrally authorised medicine containing fentanyl, was authorised in 2009.

The MAH submitted an application for a second renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

- Based on the review of the available pharmacovigilance data for Instanyl (fentanyl) and the CHMP Rapporteur's assessment report, the PRAC considered that the second renewal of the marketing authorisation could be granted with unlimited validity.
- Nevertheless, the PRAC highlighted the remaining concerns regarding safety data on misuse, abuse, off label use, dependence, overdose, accidental exposure and medication error recognized as important risks with fentanyl as well as respiratory and cardiovascular depression and local tolerability. In order to reduce the risk of off label use, the PRAC supported an update of the existing educational material to include a greater emphasis for off-label use and the serious risks of misuse and abuse which can lead to addiction, overdose and death and to better target pharmacists and patients. The Committee also supported an improvement of digital access to education with introduction of QR⁴⁸ codes to provide an easy way to access websites to healthcare professionals. In addition, the PRAC confirmed the need for a PASS (as a category 3 study in the RMP) to assess the impact of the updated educational material.
- The PRAC also supported requesting the MAH to submit to EMA, within 90 days, an update of the RMP to introduce the information on changes to existing educational material and PASS and to discuss the need to restrict the utilisation of Instanyl (fentanyl) to a particular setting.

8.3.2. Nintedanib - VARGATEF (CAP) - EMEA/H/C/002569/R/0025 (with RMP)

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Agni Kapou

Scope: 5-year renewal of the marketing authorisation

Background

Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and β) and fibroblast growth factor receptors (FGFR 1-3) kinase activity, indicated as Vargatef, in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

Vargatef, a centrally authorised medicine containing nintedanib, was authorised in 2014.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

⁴⁸ Quick response code

- Based on the review of the available pharmacovigilance data for Vargatef (nintedanib) and the CHMP Rapporteur's assessment report, the PRAC considered that the renewal of the marketing authorisation could be granted with unlimited validity.
- The PRAC advised that the MAH continues to submit PSURs on a yearly frequency in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

9.2. Ongoing or concluded pharmacovigilance inspections

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the minutes.

9.3. Others

None

10. Other safety issues for discussion requested by the CHMP or the EMA

10.1. Safety related variations of the marketing authorisation

- 10.1.1. Duloxetine - CYMBALTA (CAP) - EMEA/H/C/000572/WS1527/0078/G; DULOXETINE LILLY (CAP) - EMEA/H/C/004000/WS1527/0014/G; XERISTAR (CAP) - EMEA/H/C/000573/WS1527/0081/G; YENTREVE (CAP) - EMEA/H/C/000545/WS1527/0063/G

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: PRAC consultation on the proposed product information amendments for the following grouped variations consisting of: 1) update of sections 4.4 and 4.6 of the SmPC in order to add a warning on the risk of postpartum haemorrhage based on the final results from study F1J-MC-B057 (listed as a category 3 study in the RMP): an observational study to assess maternal and foetal outcomes following exposure to duloxetine. The package leaflet is updated accordingly; 2) enrolment termination for study F1J-MC-B034 (study B034): pregnancy registry to compare the pregnancy and birth outcomes of women given duloxetine during pregnancy with those of an unexposed group of pregnant women. The RMP (version 13) is updated accordingly. In addition, the MAH took the opportunity to correct the term 'sucrase-isomaltase' in section 4.4 of the SmPC in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and to bring the product information (PI) in line with the latest quality review of documents (QRD) template (version 10). Finally, the MAH

proposed to combine into a single SmPC the Xeristar 30 mg SmPC, Xeristar 60 mg SmPC and the Yentreve 20 mg SmPC and Yentreve 40 mg SmPC respectively, following the policy on combined SmPCs (EMA/333423/2015)

See also 15.3.5.

Background

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor, indicated as Cymbalta, Duloxetine Lilly, Xeristar and Yentreve, for the treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder.

A type II variation proposing to update the product information of Cymbalta (duloxetine), Duloxetine Lilly (duloxetine), Xeristar and Yentreve (duloxetine) based on the final results from study F1J-MC-B057 (listed as a category 3 study in the RMP): an observational study to assess maternal and foetal outcomes following exposure to duloxetine, is under evaluation at the CHMP. The PRAC was requested to provide advice on this variation.

Summary of advice

- Based on the review of the available information, the PRAC considered that the study findings are robust due to in particular a thorough design with careful control for confounding and extensive sensitivity analyses. The PRAC advised that the product information should be updated to include the risk of postpartum haemorrhage, subject to further clarification of the wording. The PRAC considered that the amendment in relation to postpartum haemorrhage for duloxetine may not be generalised to the whole class as no review has been conducted for the other substances.
- In addition, the PRAC considered that the study generated clinical data of relevance for use of duloxetine during pregnancy. The PRAC advised to request the MAH to provide a further proposal for an update of the product information as regards postpartum haemorrhage and a proposal to amend all relevant sections of the product information to add the findings from B057 study. The PRAC also requested clarifications on the risk of spontaneous abortion and requested the MAH to provide the results and a discussion on the final study report of study F1J-MC-B059, a Nordic based retrospective cohort registry-based study to investigate malformations and non-live birth outcomes. Consequently, based on the evaluation of the above data, the MAH is requested to discuss whether an update of the current recommendation that duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus is warranted, and should consider a direct healthcare professional communication (DHPC) to inform healthcare professionals (HCPs).

10.2. Timing and message content in relation to Member States' safety announcements

None

10.3. Other requests

None

10.4. Scientific Advice

Information related to this section cannot be released at the present time as it is deemed to

contain commercially confidential information.

11. Other safety issues for discussion requested by the Member States

11.1. Safety related variations of the marketing authorisation

None

11.2. Other requests

11.2.1. Abciximab (NAP) - UK/H/PSUFU/00000014/201711

Applicant(s): Janssen Biologics B.V. (ReoPro)

PRAC Lead: Patrick Batty

Scope: PRAC consultation on a PSUR follow-up (PSU FU) procedure on the review of cases of profound delayed thrombocytopenia as discussed at PRAC and agreed by CMDh following the conclusion of the PSUSA procedure on abciximab (PSUSA/00000014/201711) concluded in July 2018, on request of the United Kingdom

Background

Abciximab is an inhibitor of platelet aggregation indicated as an adjunct to heparin and acetylsalicylic acid for the prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention and for the short-term reduction of the risk of myocardial infarction in patients with unstable angina under certain conditions.

Following the evaluation of the most recently submitted PSURs for the above mentioned medicine(s), the PRAC requested the MAH to submit further data on cases of delayed thrombocytopenia (for background, see [PRAC minutes July 2018](#)). In the context of the evaluation of the responses, the United Kingdom as the lead Member State (LMS) requested PRAC advice on its assessment.

Summary of advice

- Based on the review of the available information, the PRAC supported the LMS conclusions and agreed that the product information of abciximab-containing products should be updated to include a warning on the need of regular monitoring of platelet counts for at least two weeks. The PRAC also supported the need for close monitoring of cases of profound delayed thrombocytopenia occurring with a time to onset >2 weeks and requested the MAH to provide a further cumulative review of these cases in the next PSUR.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC meeting dates 2020-2021 - amendment

The EMA Secretariat presented to PRAC a proposal to amend the PRAC plenary meeting

dates for September 2020 and September 2021, in order to move the start of the meeting to Monday. The PRAC agreed with the proposal.

Post-meeting note: On 21/05/2019, the amended PRAC plenary meeting dates for September 2020 and September 2021 were published on the [EMA website](#).

12.1.2. PRAC working group - Best practice guide on using PRAC plenary time efficiently and effectively – update on the implementation of quantitative goals

PRAC lead: Martin Huber, Ulla Wändel Liminga, Menno van der Elst, Tatiana Magálová, Ghania Chamouni, Jan Neuhauser

In line with the adopted PRAC best practice guidance (BPG) on Committee efficiency (see [PRAC minutes May 2016](#) and [PRAC minutes June 2018](#)) and the adopted implementation plan for the BPG including goals to measure compliance with the recommendations (see [PRAC minutes June 2016](#) and [PRAC minutes June 2018](#)), the PRAC was updated at the organisational matters teleconference held on 28 February 2019 on quantitative measures collected for the fourth 2018 quarter of PRAC meetings. For previous update, see [PRAC minutes February 2019](#).

12.2. Coordination with EMA Scientific Committees or CMDh-v

None

12.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

12.3.1. Healthcare Professionals Working Party (HCPWP) and Patients and Consumers Working Party (PCWP) - Nomination of PRAC representative(s)

The PRAC was invited to nominate its representatives to the Healthcare Professionals Working Party (HCPWP) and the Patients and Consumers Working Party (PCWP), which monitor the progress of the interaction with patients, consumers and healthcare professionals and help to further identify gaps and priorities in the overall interaction. At the organisational matters teleconference held on 25 April 2019, the PRAC nominated Raymond Anderson as the representative for the HCPWP and Virginie Hivert as the representative to the PCWP.

12.4. Cooperation within the EU regulatory network

None

12.5. Cooperation with International Regulators

None

12.6. Contacts of the PRAC with external parties and interaction with the Interested Parties to the Committee

None

12.7. PRAC work plan

None

12.8. Planning and reporting

12.8.1. EU Pharmacovigilance system – quarterly workload measures and performance indicators – Q1 2019 and predictions

At the organisational matters teleconference held on 25 April 2019, the EMA Secretariat presented quarterly figures on the EMA pharmacovigilance system-related workload and performance indicators. For previous update, see [PRAC minutes January 2019](#).

12.8.2. Marketing authorisation applications (MAA) forecast for 2019 – planning update dated Q1 2019

The EMA Secretariat presented to PRAC for information a quarterly updated report on marketing authorisation applications planned for submission (the business 'pipeline'). For previous update, see [PRAC minutes January 2019](#).

12.8.3. PRAC workload statistics – Q1 2019

The EMA secretariat presented, at the organisational matters teleconference held on 25 April 2019, quarterly and cumulative figures to estimate the evolution of the workload of the PRAC, by reflecting on the number of procedures and agenda items covered at each PRAC plenary meeting. For previous update, see [PRAC minutes February 2019](#).

12.9. Pharmacovigilance audits and inspections

12.9.1. Pharmacovigilance systems and their quality systems

None

12.9.2. Pharmacovigilance inspections

None

12.9.3. Pharmacovigilance audits

None

12.10. Periodic safety update reports (PSURs) & Union reference date (EURD) list

12.10.1. Periodic safety update reports

None

12.10.2. Granularity and Periodicity Advisory Group (GPAG)

PRAC lead: Menno van der Elst, Maia Uusküla

The PRAC was updated on the activities of the GPAG, focussing on harmonising and streamlining the EURD list, and noted the GPAG progress highlights. In particular, the PRAC was updated on the development of the EURD tool.

12.10.3. PSURs repository

None

12.10.4. Union reference date list – consultation on the draft list

The PRAC endorsed the draft revised EURD list, version April 2019, reflecting the PRAC's comments impacting on the data lock point (DLP) and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see [PRAC minutes April 2013](#)).

Post-meeting note: following the PRAC meeting of April 2019, the updated EURD list was adopted by the CHMP and CMDh at their April 2019 meetings and published on the EMA website on 30/04/2019, see:

[Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports \(PSURs\)](#)

12.11. Signal management

12.11.1. Signal management – feedback from Signal Management Review Technical (SMART) Working Group

PRAC lead: Menno van der Elst

The PRAC was updated on the outcome of the SMART Working Group (SMART WG) Processes meeting held on 8 April 2019. The SMART WG discussed the findings of a recent audit of signal management at the EMA, highlighting the network collaboration and transparency among its strengths. The WG also noted the progress in allocating lead Member States (LMS) for work-sharing in signal management, the reallocation of substances due to the UK's planned withdrawal from the European Union, and the practical arrangements for sharing updated information on previously validated signals in the European pharmacovigilance issues tracking tool (EPITT).

12.12. Adverse drug reactions reporting and additional monitoring

12.12.1. Management and reporting of adverse reactions to medicinal products

None

12.12.2. Additional monitoring

None

12.12.3. List of products under additional monitoring – consultation on the draft list

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 26/04/2019 on the EMA website (see: [Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring](#)).

12.13. EudraVigilance database

12.13.1. Activities related to the confirmation of full functionality

None

12.14. Risk management plans and effectiveness of risk minimisations

12.14.1. Risk management systems

None

12.14.2. Tools, educational materials and effectiveness measurement of risk minimisations

None

12.15. Post-authorisation safety studies (PASS)

12.15.1. Post-authorisation Safety Studies – imposed PASS

None

12.15.2. Post-authorisation Safety Studies – non-imposed PASS

None

12.16. Community procedures

12.16.1. Referral procedures for safety reasons

None

12.17. Renewals, conditional renewals, annual reassessments

None

12.18. Risk communication and transparency

12.18.1. PRAC meeting highlights – proposal for revision

The EMA Secretariat presented to PRAC a proposal for amending the current layout of the

PRAC meeting highlights, which are published the following working day after the end of the plenary meeting. The PRAC agreed on the importance of adequate communication about the safety of medicines and noted the aim to roll out the new infographic in May 2019.

Post-meeting note: On 17 May 2019, the May 2019 PRAC meeting highlights including infographic information was published on the EMA website.

12.18.2. Public participation in pharmacovigilance

None

12.18.3. Safety communication

None

12.19. Continuous pharmacovigilance

12.19.1. Incident management

None

12.20. Others

12.20.1. Annex II conditions and specific obligations – process proposal for earlier review

The EMA Secretariat presented to PRAC a proposal for a process for earlier review of Annex II of the product information (conditions and specific obligations to be imposed on the marketing authorisation), by incorporating it into product information revision(s) during the review of marketing authorisation applications (MAAs). This will ensure an earlier review of the information reflected in the document facilitating agreement of more robust conditions and risk minimisation activities. The PRAC supported this change in the process.

12.20.2. Opioids abuse, misuse and dependence - establishment of an oversight group

PRAC lead: Ghania Chamouni

The PRAC was informed of the establishment of an oversight group on the abuse, misuse and dependence on opioid medicines, comprising EMA and its scientific Committees as well as CMDh, EU National Competent Authorities (NCAs), EMCDDA⁴⁹ and European public health bodies. The group is set up with the aim of monitoring, information exchange, preparedness strategies and co-ordination of activities at EU level.

13. Any other business

None

⁴⁹ European Monitoring Centre for Drugs and Drug Addiction, www.emcdda.europa.eu

14. Annex I – Signals assessment and prioritisation⁵⁰

14.1. New signals detected from EU spontaneous reporting systems

As per agreed criteria for new signal(s), the PRAC adopted without further plenary discussion the recommendation of the Rapporteur to request MAH(s) to submit a cumulative review following standard timetables⁵¹.

14.1.1. Ibrutinib – IMBRUVICA (CAP)

Applicant(s): Janssen-Cilag International
PRAC Rapporteur: Nikica Mirošević Skvrce
Scope: Signal of ischemic stroke
EPITT 19369 – New signal
Lead Member State(s): HR

14.1.2. Pembrolizumab – KEYTRUDA (CAP)

Applicant(s): Merck Sharp & Dohme B.V.
PRAC Rapporteur: Menno van der Elst
Scope: Signal of optic neuritis
EPITT 19381 – New signal
Lead Member State(s): NL

14.1.3. Perampanel – FYCOMPA (CAP)

Applicant(s): Eisai GmbH
PRAC Rapporteur: Julie Williams
Scope: Signal of hepatotoxicity
EPITT 19383 – New signal
Lead Member State(s): UK

14.1.4. Ticagrelor – BRILIQUE (CAP)

Applicant(s): AstraZeneca AB
PRAC Rapporteur: Menno van der Elst
Scope: Signal of severe cutaneous adverse reactions (SCARs)

⁵⁰ Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

⁵¹ Either MA(s)'s submission within 60 days followed by a 60 day-timetable assessment or MAH's submission cumulative review within an ongoing or upcoming PSUR/PSUSA procedure (if the DLP is within 90 days), and no disagreement has been raised before the meeting

EPITT 19375 – New signal

Lead Member State(s): NL

14.2. New signals detected from other sources

14.2.1. Benralizumab – FASENRA (CAP)

Applicant(s): AstraZeneca AB

PRAC Rapporteur: David Olsen

Scope: Signal of pneumonia

EPITT 19368 – New signal

Lead Member State(s): NO

14.2.2. Omalizumab – XOLAIR (CAP)

Applicant(s): Novartis Europharm Limited

PRAC Rapporteur: Annika Folin

Scope: Signal of acquired haemophilia

EPITT 19385 – New signal

Lead Member State(s): SE

14.2.3. Teriflunomide – AUBAGIO (CAP)

Applicant(s): Sanofi-aventis groupe

PRAC Rapporteur: Martin Huber

Scope: Signal of psoriasis

EPITT 19366 – New signal

Lead Member State(s): DE

15. Annex I – Risk management plans

15.1. Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance(s) will be made available following the CHMP opinion on their marketing authorisation(s).

15.1.1. Fluticasone furoate, umecclidinium, vilanterol - EMEA/H/C/005254

Scope: Treatment of adult patients with chronic obstructive pulmonary disease (COPD)

15.2. Medicines in the post-authorisation phase – PRAC-led procedures

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the variation procedure for the below mentioned medicine(s).

15.2.1. Abacavir - ZIAGEN (CAP) - EMEA/H/C/000252/WS1521/0105; abacavir, lamivudine - KIVEXA (CAP) - EMEA/H/C/000581/WS1521/0079; abacavir, lamivudine, zidovudine - TRIZIVIR (CAP) - EMEA/H/C/000338/WS1521/0112

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Submission of a RMP (version 1.0) combining the RMPs for Ziagen (abacavir), Kivexa (abacavir/lamivudine) and Trizivir (abacavir/lamivudine/zidovudine) into one RMP specific to abacavir-active substance and revision of the important identified/potential risk for abacavir-containing products in line with revision 2 of GVP module V on 'Risk management systems', based on the post-marketing data

15.2.2. Cangrelor - KENGREXAL (CAP) - EMEA/H/C/003773/II/0015

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Amelia Cupelli

Scope: Update of the RMP (version 2.0) in order to update the requirements for a planned study (listed as a category 3 in the RMP): a multicentre, observational, non-interventional European study of patients undergoing percutaneous coronary intervention (PCI) who receive cangrelor and transition to either clopidogrel, prasugrel or ticagrelor. In addition, the MAH took the opportunity to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.2.3. Carfilzomib - KYPROLIS (CAP) - EMEA/H/C/003790/II/0034, Orphan

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: Update of the RMP (version 10) in line with revision 2 of GVP module V on 'Risk management systems', resulting in the reclassification and removal of a number of identified and potential risks and missing information

15.2.4. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0078/G

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of an update of the RMP (version 25) in order to: 1) bring it in line with revision 2 of GVP module V on 'Risk management systems'; 2) add study 20170534 (listed as category 3 study in the RMP): an open-label extension of the currently ongoing study 20130173 involving paediatric subjects with osteogenesis imperfecta, based on the MAH's commitment arising from Prolia (denosumab) approved

paediatric investigation plan (PIP: EMEA-000145-PIP02-12): open-label, prospective, extension study; 3) add a study (listed as category 3 study in the RMP) to further characterize potential increased risk of cerebrovascular events (stroke) and other serious cardiovascular events in subjects with osteoporosis, as per the conclusion of periodic safety update single assessment (PSUSA) procedure PSUSA/00000954/201709 adopted in April 2018

15.2.5. Denosumab - PROLIA (CAP) - EMEA/H/C/001120/II/0081

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 26) in order to amend the study population to men and women who receive denosumab with glucocorticoid exposure and related study objectives for study 20090522 (listed as a category 3 study in the RMP): denosumab global safety assessment among women with postmenopausal osteoporosis and men with osteoporosis in multiple observational databases. The amended protocol for study 20090522 is provided accordingly

15.2.6. Infliximab - FLIXABI (CAP) - EMEA/H/C/004020/II/0039

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Update of the RMP (version 9.0) to replace the current registries with one company-sponsored initiated registry, PERFUSE: one-year persistence to treatment of patients receiving Flixabi (infliximab): a French cohort study; together with three inflammatory bowel disease (IBD) registries, namely: long-term observation registry in German IBD patients (CEDUR), Czech registry of IBD patients on biological therapy (CREDIT) and Dutch network of hospitals IBD registry (DREAM)

15.2.7. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/II/0062

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Update of the RMP (version 13.5) in order to introduce a patient information brochure (PIB) as an additional risk minimisation measure (aRMM). Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' is updated accordingly

15.2.8. Pramipexole - MIRAPEXIN (CAP) - EMEA/H/C/000134/WS1510/0089; SIFROL (CAP) - EMEA/H/C/000133/WS1510/0080

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Update of the RMP (version 9) to implement changes requested in the conclusions of periodic safety update single assessment (PSUSA) PSUSA/00002491/201604 procedure and in connection with a PRAC signal assessment procedure. In addition, the RMP is updated in

order to bring it in line with revision 2 of the guidance on the format of RMP in the EU (template). Furthermore, the MAH took the opportunity to adapt the medical search strategies and data retrieval approach without any impact on the overall safety conclusion

15.2.9. Semaglutide - OZEMPIC (CAP) - EMEA/H/C/004174/II/0006

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Annika Folin

Scope: Update of the RMP (version 3.0) in order to reflect that the first milestones (i.e. final protocol submissions) are fulfilled for study NN9535-4447: a cohort study based on Nordic registry data to assess the risk of pancreatic cancer associated with the use of Ozempic (semaglutide) in patients with type 2 diabetes mellitus (T2DM) and study NN9535-4352: a randomised, double-masked parallel-group, placebo-controlled trial assessing the long-term effects of Ozempic (semaglutide) on diabetic retinopathy in subjects with T2DM. In addition, the RMP is updated in line with revision 2 of GVP module V on 'Risk management systems' and in line with revision 2 of the guidance on the format of RMP in the EU (template)

15.3. Medicines in the post-authorisation phase – CHMP-led procedures

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the updated versions of the RMP for the below mentioned medicine(s).

15.3.1. Atezolizumab - TECENTRIQ (CAP) - EMEA/H/C/004143/II/0022

Applicant: Roche Registration GmbH

PRAC Rapporteur: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Update of sections 4.2 and 5.2 of the SmPC in order to add two dosing regimens: 840 mg every 2 weeks and 1680 mg every 4 weeks administered as an intravenous (IV) infusion for the approved indications, based on results of population pharmacokinetics modelling and simulation analyses (report No. 1085557) and supported by exposure-response analyses (report No. 1087176). The package leaflet is updated accordingly. In addition, the RMP is updated (version 4.2) in order to reflect the proposed new dosing regimens and in order to align the indication statement for metastatic urothelial carcinoma with the SmPC. Moreover, the due date for submission of RMP commitments and an Annex II condition are proposed to be updated

15.3.2. Bevacizumab - AVASTIN (CAP) - EMEA/H/C/000582/II/0106/G

Applicant: Roche Registration GmbH

PRAC Rapporteur: Anette Kirstine Stark

Scope: Grouped variations consisting of: 1) update of section 5.1 of the SmPC to reflect final overall survival data from the long-term follow-up study JO25567 (erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer (NSCLC) harbouring epidermal growth factor receptor (EGFR) mutations: an open-label, randomised, multicentre, phase 2 study) in order to fulfil ANX 085 for study JO29424 (survival follow up of JO25567); 2) change in the deadline for the fulfilment of

ANX 086 (discussion on any further outcome data on the combination of bevacizumab and erlotinib in the first-line treatment of patients with non-squamous NSCLC harbouring EGFR activating mutations) from Q4 2018 to Q2 2019. Annex II-D on 'conditions or restrictions with regard to the safe and effective use of the medicinal product' and the RMP (version 29.0) are updated accordingly. The RMP is submitted in line with revision 2 of the guidance on the format of RMP in the EU (template) and consolidates the approved versions (versions 27.1 and 28.1)

15.3.3. [Ciclosporin - IKERVIS \(CAP\) - EMEA/H/C/002066/WS1490/0014; VERKAZIA \(CAP\) - EMEA/H/C/004411/WS1490/0001](#)

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Update of the RMP (version 7.0) in order to bring the RMP in line with revision 2 of the guidance on the format of RMP in the EU (template). The milestones for the Verkazia (ciclosporin) PASS on: quantification of the risk of periocular skin cancer, conjunctival or corneal neoplasia in children treated with Verkazia (ciclosporin) for vernal keratoconjunctivitis (VKC), have also been updated. In addition, the MAH proposed to align Ikervis (ciclosporin) SmPC section 4.4 on concomitant therapy and effects on immune system with Verkazia (ciclosporin) SmPC in order to harmonise the routine risk minimisation measures for both medicinal products. The MAH took this opportunity to implement the latest quality review of documents (QRD) template and the safety features for Ikervis (ciclosporin)

15.3.4. [Dapagliflozin - EDISTRIDE \(CAP\) - EMEA/H/C/004161/WS1539/0029; FORXIGA \(CAP\) - EMEA/H/C/002322/WS1539/0048; dapagliflozin, metformin - EBYMECT \(CAP\) - EMEA/H/C/004162/WS1539/0035; XIGDUO \(CAP\) - EMEA/H/C/002672/WS1539/0046](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Worksharing variations consisting of an update of sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC of Forxiga (dapagliflozin), Edistride (dapagliflozin), Xigduo (dapagliflozin/metformin) and Ebymect (dapagliflozin/metformin) in order to modify the current indication for improvement of glycaemic control based on final results from study D1693C00001 (DECLARE) (listed as a category 3 study in the RMP): 'dapagliflozin effect on cardiovascular events a multicentre, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes' for the prevention of new or worsening heart failure (HF) or cardiovascular (CV) death and for the prevention of new or worsening nephropathy. The package leaflets are updated accordingly. The RMPs for Edistride and Forxiga (version 17) and Ebymect and Xigduo (version 11) are updated accordingly. In addition, the MAH took the opportunity to update the warning on lactose in accordance with the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use'. The MAH also took the opportunity to introduce minor editorial changes in the product information

15.3.5. [Duloxetine - CYMBALTA \(CAP\) - EMEA/H/C/000572/WS1527/0078/G; DULOXETINE LILLY \(CAP\) - EMEA/H/C/004000/WS1527/0014/G; XERISTAR \(CAP\) - EMEA/H/C/000573/WS1527/0081/G; YENTREVE \(CAP\) - EMEA/H/C/000545/WS1527/0063/G](#)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped variations consisting of: 1) update of sections 4.4 and 4.6 of the SmPC in order to add a warning on the risk of postpartum haemorrhage based on the final results from study F1J-MC-B057 (listed as a category 3 study in the RMP): an observational study to assess maternal and foetal outcomes following exposure to duloxetine. The package leaflet is updated accordingly; 2) enrolment termination for study F1J-MC-B034 (study B034): pregnancy registry to compare the pregnancy and birth outcomes of women given duloxetine during pregnancy with those of an unexposed group of pregnant women. The RMP (version 13) is updated accordingly. In addition, the MAH took the opportunity to correct the term 'sucrase-isomaltase' in section 4.4 of the SmPC in line with the Annex to the European Commission (EC) guideline on 'excipients in the labelling and package leaflet of medicinal products for human use' and to bring the product information (PI) in line with the latest quality review of documents (QRD) template (version 10). Finally, the MAH proposed to combine into a single SmPC the Xeristar 30 mg SmPC, Xeristar 60 mg SmPC and the Yentreve 20 mg SmPC and Yentreve 40 mg SmPC respectively, following the policy on combined SmPCs (EMA/333423/2015)

See also 10.1.1.

15.3.6. [Eculizumab - SOLIRIS \(CAP\) - EMEA/H/C/000791/II/0105, Orphan](#)

Applicant: Alexion Europe SAS

PRAC Rapporteur: Eva Segovia

Scope: Extension of indication to include treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody (Ab) positive. As a consequence the SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, Annex II are updated. The package leaflet and the RMP (version 19) are updated accordingly

15.3.7. [Guanfacine - INTUNIV \(CAP\) - EMEA/H/C/003759/II/0015](#)

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Update of section 4.5 of the SmPC in order to remove the statement on potential drug interactions with drugs that inhibit organic cation transporter 1 (OCT1) based on the final results from study V8953M-SPD503: a non-clinical study on transporter interaction - OCT1 inhibition. The RMP (version 3.0) is updated accordingly

15.3.8. [Human normal immunoglobulin - FLEBOGAMMA DIF \(CAP\) - EMEA/H/C/000781/II/0059/G](#)

Applicant: Instituto Grifols, S.A.

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Grouped variations consisting of: 1) update of section 4.8 of the SmPC for Flebogamma DIF (human normal immunoglobulin) 100 mg/mL in order to update the safety information based on the final results from study IG0601: A multicentre, prospective, open-label, clinical trial to assess the safety and the efficacy of a new intravenous immune globulin (IGIV3I Grifols 10%) in patients with idiopathic (immune) thrombocytopenic purpura. The package leaflet is updated accordingly; 2) update of section 4.8 of the SmPC to revise the adverse drug reactions for both strengths based on all completed studies previously submitted. The package leaflet is updated accordingly; 3) update of SmPC according to the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) which came into effect on 01 January 2019. The package leaflet and the RMP (version 7.0) are updated accordingly

15.3.9. Insulin aspart - FIASP (CAP) - EMEA/H/C/004046/II/0010

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Amelia Cupelli

Scope: Extension of indication to include treatment of children and adolescents aged 1 year and above based on data from study NN1218-4101: a phase 3b study on efficacy and safety of faster-acting insulin aspart compared to Novorapid (insuplin aspart) both in combination with insulin degludec in children and adolescents with type 1 diabetes; supported by data from study NN1218-4371: a trial comparing the pharmacokinetic properties of fast-acting insulin aspart between children, adolescents and adults with type 1 diabetes; and study NN1218-3888: a trial investigating the pharmacokinetic properties of Fiasp (insulin aspart) in children, adolescents and adults with type 1 diabetes. As a consequence, sections 4.1, 4.2, 4.8, and 5.1 of the SmPC and the corresponding sections of the package leaflet are updated accordingly. In addition, the MAH took the opportunity to introduce other non-related minor or editorial changes throughout the product information to increase readability/consistency

15.3.10. Insulin lispro - HUMALOG (CAP) - EMEA/H/C/000088/X/0169

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Line extension application. The RMP is updated (version 9.3) accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.11. Insulin lispro - LIPROLOG (CAP) - EMEA/H/C/000393/X/0130

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Annika Folin

Scope: Line extension application. The RMP is updated (version 9.3) accordingly and in line with revision 2 of GVP module V on 'Risk management systems'

15.3.12. Ivacaftor - KALYDECO (CAP) - EMEA/H/C/002494/X/0075/G, Orphan

Applicant: Vertex Pharmaceuticals (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Grouped applications consisting of: 1) extension application to add a new strength of 25 mg granules in sachet in the treatment of cystic fibrosis in children aged 6 to less than 12 months old; 2) update of sections 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC, and sections 2 and 3 of the package leaflet for the 150 mg film-coated tablet presentation to bring it in line with the new dosage form (25 mg granules). The RMP (version 8.3) is updated accordingly. In addition, the MAH took the opportunity to implement minor updates in the product information

15.3.13. Lacosamide - VIMPAT (CAP) - EMEA/H/C/000863/II/0073/G

Applicant: UCB Pharma S.A.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Grouped variations consisting of: 1) update of sections 4.4, 4.5 and 4.8 of the SmPC in order to include new safety information on cardiac arrhythmias based on safety signal assessment report (SSAR); 2) update of section 4.8 of the SmPC to update the frequency of some adverse events (AEs) based on data obtained from the updated safety pool analysis (Pool DBC-1) which consists of the combined data from SP667, SP754, SP755, and EP0008. All of these studies were randomized, double-blind, placebo-controlled, parallel-group, adjunctive therapy studies in subjects with epilepsy. The package leaflet and the RMP (version 13.0) are updated accordingly

15.3.14. Pembrolizumab - KEYTRUDA (CAP) - EMEA/H/C/003820/II/0069

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Extension of indication to include first line treatment of advanced or metastatic renal cell carcinoma (RCC) as combination therapy of pembrolizumab together with axitinib based on the results of the first interim analysis (IA1) from pivotal study KN426: an ongoing, phase 3, randomized, open-label, multicentre, global study to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib in previously untreated subjects with advanced/metastatic RCC. It also includes supportive data from KEYNOTE-427 Cohort A (pembrolizumab monotherapy): pembrolizumab monotherapy as first-line therapy in advanced clear cell RCC (ccRCC) and sponsored study A4061051 (axitinib monotherapy): axitinib for the treatment of metastatic RCC. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The package leaflet and the RMP (version 24.1) are updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the package leaflet

15.3.15. Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted) - MOSQUIRIX (Art 58⁵²) - EMEA/H/W/002300/II/0036

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Jean-Michel Dogné

Scope: Update of section 4.4 of the SmPC in order to modify the warning on 'protection

⁵² Article 58 of Regulation (EC) No 726/2004 allows the Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organisation (WHO) on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)

against *Plasmodium falciparum* malaria' over time. This update is based on the final results from study MALARIA-076 (listed as a category 3 study in the RMP): an open extension to phase 3, multicentre study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of Mosquirix (plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)) malaria vaccine in infants and children. The RMP (version 4.1) is updated accordingly

15.3.16. Selexipag - UPTRAVI (CAP) - EMEA/H/C/003774/II/0022

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Update of Sections 4.2, 4.4 and 4.5 of the SmPC in order to update the safety information based on the final results from study AC-065-117 (listed as a category 3 study in the RMP): clinical pharmacology drug-drug interaction (DDI) study evaluating the effect of clopidogrel a moderate inhibitor of CYP2C8⁵³, on the pharmacokinetics of selexipag and its active metabolite ACT-333679. The package leaflet and the RMP (version 6.1) are updated accordingly. In addition, the MAH took the opportunity to correct minor discrepancies in the SmPC

15.3.17. Smallpox vaccine (live modified vaccinia virus Ankara) - IMVANEX (CAP) - EMEA/H/C/002596/II/0036

Applicant: Bavarian Nordic A/S

PRAC Rapporteur: Julie Williams

Scope: Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information and to provide confirmation in terms of immunogenicity based on the results from study POX-MVA-006 (listed as an obligation in Annex II (ANX 004)): a randomized, open-label phase 3 non-inferiority trial to compare indicators of efficacy for smallpox vaccine to the US licensed replicating smallpox vaccine in 18-42 year old healthy vaccinia-naïve subjects. The package leaflet and the RMP (version 7.2) are updated accordingly

15.3.18. Sofosbuvir - SOVALDI (CAP) - EMEA/H/C/002798/WS1518/0055; sofosbuvir, ledipasvir - HARVONI (CAP) - EMEA/H/C/003850/WS1518/0077; sofosbuvir, velpatasvir - EPCLUSA (CAP) - EMEA/H/C/004210/WS1518/0034; sofosbuvir, velpatasvir, voxilaprevir - VOSEVI (CAP) - EMEA/H/C/004350/WS1518/0025

Applicant: Gilead Sciences Ireland UC

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Worksharing variation to update sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Epclusa (sofosbuvir/velpatasvir) and Harvoni (sofosbuvir/ledipasvir), sections 4.2, 4.4, 5.1 and 5.2 for Sovaldi (sofosbuvir) and sections 4.2, 4.8 and 5.2 for Vosevi (sofosbuvir/velpatasvir/voxilaprevir) in order to add new information regarding the use of sofosbuvir-containing products in patients with renal impairment, based on the final results from studies: 1) GS-US-342-4062 (listed as a category 3 study in the RMP): a phase 2,

⁵³ Cytochrome P450 2C8

multicentre, open-label study to evaluate the efficacy and safety of sofosbuvir/velpatasvir for 12 weeks in subjects with chronic hepatitis C virus (HCV) infection who are on dialysis for end stage renal disease; 2) GS-US-337-4063 (listed as a category 3 study in the RMP): a phase 2, multicentre, open-label study to evaluate the efficacy and safety of ledipasvir/sofosbuvir in subjects with genotype 1, 4, 5 and 6 chronic HCV infection who are on dialysis for end stage renal disease; 3) GS-US-334-0154 (listed as a category 3 study in the RMP): a phase 2b, open label study of 200 mg or 400 mg Sofosbuvir+ribavirin for 24 weeks in genotype 1 or 3 HCV infected subjects with renal insufficiency; 4) study GS-US-338-1125: a phase 1, open-label, parallel-group, single-dose study to evaluate the pharmacokinetics of voxilaprevir in subjects with normal renal function and severe renal impairment. The package leaflet is updated accordingly. The RMPs for Eplclusa (version 4.1), Harvoni (version 5.1), Sovaldi (version 8.1) and Vosevi (version 2.1) are updated accordingly

16. Annex I - Periodic safety update reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated in the outcome of the relevant PSUR/PSUSA procedure(s).

16.1. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) only

16.1.1. Aliskiren - RASILEZ (CAP); aliskiren, hydrochlorothiazide - RASILEZ HCT (CAP) - PSUSA/00000089/201809

Applicant: Noden Pharma DAC

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.2. Ciclosporin⁵⁴ - IKERVIS (CAP); VERKAZIA (CAP) - PSUSA/00010362/201809

Applicant: Santen Oy

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.1.3. Daptomycin - CUBICIN (CAP) - PSUSA/00000931/201809

Applicant: Merck Sharp & Dohme B.V.

⁵⁴ Topical use only

PRAC Rapporteur: Karen Pernille Harg

Scope: Evaluation of a PSUSA procedure

16.1.4. Darunavir, cobicistat, emtricitabine, tenofovir alafenamide - SYMTUZA (CAP) - PSUSA/00010646/201809

Applicant: Janssen-Cilag International N.V.

PRAC Rapporteur: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.1.5. Darvadstrocel - ALOFISEL (CAP) - PSUSA/00010676/201809

Applicant: Takeda Pharma A/S, ATMP⁵⁵

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

16.1.6. Denosumab⁵⁶ - XGEVA (CAP) - PSUSA/00009119/201809

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.7. Dulaglutide - TRULICITY (CAP) - PSUSA/00010311/201809

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: Evaluation of a PSUSA procedure

16.1.8. Dupilumab - DUPIXENT (CAP) - PSUSA/00010645/201809

Applicant: Sanofi-aventis groupe

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.9. Eftrenonacog alfa - ALPROLIX (CAP) - PSUSA/00010499/201809

Applicant: Swedish Orphan Biovitrum AB (publ)

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Evaluation of a PSUSA procedure

⁵⁵ Advanced therapy medicinal product

⁵⁶ Indicated for skeletal related events associated with bone metastases and for giant cell tumour of bone only

16.1.10. Eltrombopag - REVOLADE (CAP) - PSUSA/00001205/201809

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Eva Segovia

Scope: Evaluation of a PSUSA procedure

16.1.11. Eluxadoline - TRUBERZI (CAP) - PSUSA/00010528/201809

Applicant: Allergan Pharmaceuticals International Ltd

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.12. Etravirine - INTELENCE (CAP) - PSUSA/00001335/201809

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.13. Ferric citrate coordination complex - FEXERIC (CAP) - PSUSA/00010418/201809

Applicant: Keryx Biopharma UK Ltd.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

16.1.14. Fluticasone furoate, umecclidinium, vilanterol - ELEBRATO ELLIPTA (CAP); TRELEGY ELLIPTA (CAP) - PSUSA/00010653/201809

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

16.1.15. Glycopyrronium⁵⁷ - SIALANAR (CAP) - PSUSA/00010529/201809

Applicant: Proveca Pharma Limited

PRAC Rapporteur: Zane Neikena

Scope: Evaluation of a PSUSA procedure

16.1.16. Human coagulation factor X - COAGADEX (CAP) - PSUSA/00010481/201809

Applicant: BPL Bioproducts Laboratory GmbH

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

⁵⁷ Centrally authorised product indicated for the treatment of severe siallorhea only

16.1.17. Insulin degludec, liraglutide - XULTOPHY (CAP) - PSUSA/00010272/201809

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: Evaluation of a PSUSA procedure

16.1.18. Isavuconazole - CRESEMBA (CAP) - PSUSA/00010426/201809 (with RMP)

Applicant: Basilea Pharmaceutica Deutschland GmbH

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.19. Ixekizumab - TALTZ (CAP) - PSUSA/00010493/201809

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.1.20. Mepolizumab - NUCALA (CAP) - PSUSA/00010456/201809

Applicant: GlaxoSmithKline Trading Services Limited

PRAC Rapporteur: Brigitte Keller-Stanislowski

Scope: Evaluation of a PSUSA procedure

16.1.21. Moroctocog alfa - REFACTO AF (CAP) - PSUSA/00002089/201808

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.1.22. Oritavancin - ORBACTIV (CAP) - PSUSA/00010368/201809

Applicant: Menarini International Operations Luxembourg S.A.

PRAC Rapporteur: Adam Przybylkowski

Scope: Evaluation of a PSUSA procedure

16.1.23. Panitumumab - VECTIBIX (CAP) - PSUSA/00002283/201809

Applicant: Amgen Europe B.V.

PRAC Rapporteur: David Olsen

Scope: Evaluation of a PSUSA procedure

[16.1.24. Pitolisant - WAKIX \(CAP\) - PSUSA/00010490/201809](#)

Applicant: Bioprojet Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

[16.1.25. Raltegravir - ISENTRESS \(CAP\) - PSUSA/00010373/201809](#)

Applicant: Merck Sharp & Dohme B.V.

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

[16.1.26. Ribociclib - KISQALI \(CAP\) - PSUSA/00010633/201809](#)

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

[16.1.27. Riociguat - ADEMPAS \(CAP\) - PSUSA/00010174/201809](#)

Applicant: Bayer AG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Evaluation of a PSUSA procedure

[16.1.28. Rucaparib - RUBRACA \(CAP\) - PSUSA/00010694/201809](#)

Applicant: Clovis Oncology Ireland Limited

PRAC Rapporteur: Annika Folin

Scope: Evaluation of a PSUSA procedure

[16.1.29. Sodium zirconium cyclosilicate - LOKELMA \(CAP\) - PSUSA/00010675/201809](#)

Applicant: AstraZeneca AB

PRAC Rapporteur: Kirsti Villikka

Scope: Evaluation of a PSUSA procedure

[16.1.30. Tildrakizumab - ILUMETRI \(CAP\) - PSUSA/00010720/201809](#)

Applicant: Almirall S.A

PRAC Rapporteur: Adrien Inoubli

Scope: Evaluation of a PSUSA procedure

16.1.31. Tobramycin⁵⁸ - VANTOBRA⁵⁹ - PSUSA/00010370/201809 (with RMP)

Applicant: PARI Pharma GmbH

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.1.32. Velmanase alfa - LAMZEDE (CAP) - PSUSA/00010677/201809

Applicant: Chiesi Farmaceutici S.p.A.

PRAC Rapporteur: Jan Neuhauser

Scope: Evaluation of a PSUSA procedure

16.2. PSUR single assessment (PSUSA) procedures including centrally authorised products (CAPs) and nationally authorised products (NAPs)

16.2.1. Anagrelide - ANAGRELIDE MYLAN (CAP); XAGRID (CAP); NAP - PSUSA/00000208/201809

Applicant(s): Mylan S.A.S (Anagrelide Mylan), Shire Pharmaceuticals Ireland Limited (Xagrid), various

PRAC Rapporteur: Ghania Chamouni

Scope: Evaluation of a PSUSA procedure

16.2.2. Zoledronic acid⁶⁰ - ZOLEDRONIC ACID HOSPIRA (CAP); ZOLEDRONIC ACID MEDAC (CAP); ZOMETA (CAP); NAP - PSUSA/00003149/201808

Applicant(s): Medac Gesellschaft für klinische Spezialpräparate mbH (Zoledronic acid medac), Novartis Europharm Limited (Zometa), Pfizer Europe MA EEIG (Zoledronic acid Hospira), various

PRAC Rapporteur: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

16.3. PSUR single assessment (PSUSA) procedures including nationally authorised products (NAPs) only

16.3.1. Aztreonam⁶¹ (NAP) - PSUSA/00010178/201808

Applicant(s): various

PRAC Lead: Anette Kirstine Stark

Scope: Evaluation of a PSUSA procedure

⁵⁸ Nebuliser solution, centrally authorised product(s) only

⁵⁹ European Commission (EC) decision on the MA withdrawal of Vantobra dated 18 February 2019

⁶⁰ Indicated for cancer and fractures only

⁶¹ Parenteral use only

16.3.2. Chloroquine (NAP) - PSUSA/00000685/201808

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.3. Ciclesonide (NAP) - PSUSA/00000742/201808

Applicant(s): various

PRAC Lead: Ulla Wändel Liminga

Scope: Evaluation of a PSUSA procedure

16.3.4. Dexamfetamine (NAP) - PSUSA/00000986/201809

Applicant(s): various

PRAC Lead: Ana Sofia Diniz Martins

Scope: Evaluation of a PSUSA procedure

16.3.5. Fluocinolone acetonide⁶² (NAP) - PSUSA/00010224/201808

Applicant(s): various

PRAC Lead: Marcia Sofia Sanches de Castro Lopes Silva

Scope: Evaluation of a PSUSA procedure

16.3.6. Rilmenidine (NAP) - PSUSA/00002643/201808

Applicant(s): various

PRAC Lead: Julia Pallos

Scope: Evaluation of a PSUSA procedure

16.4. Follow-up to PSUR/PSUSA procedures

16.4.1. Apixaban - ELIQUIS (CAP) - EMEA/H/C/002148/LEG 035

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Menno van der Elst

Scope: Detailed review of cases of worsening of renal function in patients using apixaban from post marketing cases, clinical trial data, and literature including cases with a possible or probable relationship due to missing information, as requested in the conclusions of the periodic safety update single assessment procedure PSUSA/00000226/201805 adopted at the December 2018 PRAC meeting (held on 26-29 November 2018)

⁶² Intravitreal implant in applicator only

17. Annex I – Post-authorisation safety studies (PASS)

Based on the assessment of the following PASS protocol(s), result(s), interim result(s) or feasibility study(ies), and following endorsement of the comments received, the PRAC adopted the conclusion of the Rapporteurs on their assessment for the medicines listed below without further plenary discussion.

17.1. Protocols of PASS imposed in the marketing authorisation(s)⁶³

17.1.1. Tisagenlecleucel - KYMRIA[®] (CAP) - EMEA/H/C/PSP/S/0066.1

Applicant: Novartis Europharm Ltd, ATMP⁶⁴

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to PSA/S/0031 [protocol for non-interventional study CCTL019B2401 with secondary use of data from two registries conducted by the 'European Society for Blood and Marrow Transplantation' (EBMT) and 'Centre for International Blood and Marrow Transplant Research' (CIBMTR) to evaluate the long term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel (chimeric antigen receptor (CAR)-T cell therapy) in a real-world setting] as per the request for supplementary information (RSI) adopted in December 2018

17.2. Protocols of PASS non-imposed in the marketing authorisation(s)⁶⁵

17.2.1. Adalimumab - AMGEVITA (CAP) - EMEA/H/C/004212/MEA 001

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Protocol for study 20160264 (ABP 501) - British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR): an observational study to evaluate long term safety of Amgevita (adalimumab) in patients with rheumatoid arthritis [final report due date: Q3 2027] (from initial MA/opinion)

17.2.2. Baricitinib - OLUMIANT (CAP) - EMEA/H/C/004085/MEA 009.1

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Adam Przybylkowski

Scope: MAH's response to MEA 009 [PASS protocol for study I4V-MC-B0166: assessment of off-label use in paediatric patients in the UK in the Clinical Practice Research Datalink (CPRD) database] as per the request for supplementary information (RSI) adopted in December 2018

⁶³ In accordance with Article 107n of Directive 2001/83/EC

⁶⁴ Advanced therapy medicinal product

⁶⁵ In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004

17.2.3. Cobimetinib - COTELLIC (CAP) - EMEA/H/C/003960/MEA 003.4

Applicant: Roche Registration GmbH

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 003.3 [protocol for study ML39302 (COVENIS) (listed as a category 3 study in the RMP): a non-interventional study to investigate the effectiveness, safety and utilisation of cobimetinib and vemurafenib in patients with and without brain metastases with BRAF V600 mutant melanoma under real world conditions (final clinical study report (CSR) due date: December 2022)] as per the request for supplementary information (RSI) adopted in November 2018

17.2.4. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 002.7

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002.6 [amendment to previously agreed protocol for study 1245.96 (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors] as per the request for supplementary information (RSI) adopted in October 2018

17.2.5. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 004.3

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 004.2 [amendment to previously agreed protocol for study 1245.96 (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors] as per the request for supplementary information (RSI) adopted in October 2018

17.2.6. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 003.4

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 003.3 [amendment to previously agreed protocol for study 1245.96 (version 5.0): an observational cohort study using existing data including urinary tract infection (UTI) as a safety topic of interest assessing a number of risks in patients treated with empagliflozin compared with patients treated with other sodium-glucose cotransporter-2 (SGLT2) inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors] as per the request for supplementary information (RSI) adopted in October 2018

17.2.7. Tildrakizumab - ILUMETRI (CAP) - EMEA/H/C/004514/MEA 003

Applicant: Almirall S.A

PRAC Rapporteur: Adrien Inoubli

Scope: Protocol for study M-14745-40: European Psoriasis Registry to collect long-term safety data for tildrakizumab and to further characterise the long-term safety profile of tildrakizumab in the treatment of psoriasis under conditions of routine clinical (from initial MAA/opinion)

17.2.8. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 045.3

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: MAH's response to MEA-045.2 [protocol for study RRA-20745: a PASS to investigate the long-term safety in adult patients with moderately to severely active Crohn's disease] as per the request for supplementary information (RSI) adopted in December 2018

17.3. Results of PASS imposed in the marketing authorisation(s)⁶⁶

None

17.4. Results of PASS non-imposed in the marketing authorisation(s)⁶⁷

17.4.1. Adalimumab - HULIO (CAP) - EMEA/H/C/004429/II/0004

Applicant: Mylan S.A.S

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from study FKB327-003 (listed as a category 3 study in the RMP): an open-label extension study to compare the long term efficacy, safety, immunogenicity and pharmacokinetics of Hulio (adalimumab) and Humira (adalimumab) in patients with rheumatoid arthritis on concomitant methotrexate (ARABESC-OLE). The RMP (version 2.0) is updated accordingly. In addition, the MAH took the opportunity to remove the product information text from Annex 6 of the RMP and proposed to only keep the text for patient alert card in the RMP as an additional risk minimisation measure

17.4.2. Adalimumab - HUMIRA (CAP) - EMEA/H/C/000481/II/0185

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Submission of the final report from the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT) registry (listed as a category 3 study in the RMP): an ongoing long-term observational cohort study initiated in Germany in 2001 by the German Society of Rheumatology to investigate the long-term safety, effectiveness, and costs of biologic

⁶⁶ In accordance with Article 107p-q of Directive 2001/83/EC

⁶⁷ In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

therapies for rheumatoid arthritis

17.4.3. Exenatide - BYDUREON (CAP) - EMEA/H/C/002020/II/0054

Applicant: AstraZeneca AB

PRAC Rapporteur: Annika Folin

Scope: Submission of the final study report, as requested by PRAC in the conclusions of MEA 11.5 adopted at the October 2016 meeting, from study H80-MC-B015 extension/D5550R00003: 'incidence of pancreatic malignancy and thyroid neoplasm in type 2 diabetes mellitus (T2DM) patients who initiate exenatide compared to other antihyperglycemic drugs' as well as the feasibility study on 'incidence of pancreatic cancer and thyroid neoplasm among T2DM who initiated Bydureon (exenatide) as compared with those who initiated other glucose lowering drugs'. The RMP (version 33) is updated accordingly

17.4.4. Fluticasone furoate, vilanterol - RELVAR ELLIPTA (CAP) - EMEA/H/C/002673/WS1568/0043; REVINTY ELLIPTA (CAP) - EMEA/H/C/002745/WS1568/0041

Applicant: GlaxoSmithKline (Ireland) Limited

PRAC Rapporteur: Maria del Pilar Rayon

Scope: Submission of the final report from study HZC102972 (listed as a category 3 study in the RMP): a PASS to further characterise the important potential risk of decreased bone mineral density (BMD) and associated fractures with fluticasone furoate (FF)/vilanterol (VI) in the treatment of chronic obstructive pulmonary disease (COPD) by evaluating the effect of the inhaled corticosteroid fluticasone furoate (FF) on bone mineral density by comparing FF/VI treatment with VI treatment in subjects with moderate COPD

17.4.5. Loxapine - ADASUVE (CAP) - EMEA/H/C/002400/II/0030

Applicant: Ferrer Internacional s.a.

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Submission of the final report from drug utilisation study AMDC-204-403 EU (listed as a category 3 study in the RMP): a multinational retrospective medical record review to evaluate utilisation patterns of Adasuve (loxapine) for inhalation in agitated persons in routine clinical care. The RMP (version 9.1) is updated accordingly

17.4.6. Teriparatide - MOVYMIA (CAP) - EMEA/H/C/004368/II/0010

Applicant: Stada Arzneimittel AG

PRAC Rapporteur: Ronan Grimes

Scope: Submission of the final clinical study report from study RGB1023031: a phase 3, multicentre, randomised, active-controlled, parallel-group, comparative study to evaluate the efficacy and safety of Movymia (teriparatide) to the originator medicinal product containing teriparatide in patients with osteoporosis at high risk of fracture. The RMP (version 1.3) is updated accordingly

17.4.7. Teriparatide - TERROSA (CAP) - EMEA/H/C/003916/II/0009

Applicant: Gedeon Richter Plc.

PRAC Rapporteur: Ronan Grimes

Scope: Submission of the final clinical study report from study RGB1023031: a phase 3, multicentre, randomised, active-controlled, parallel-group, comparative study to evaluate the efficacy and safety of Terrosa (teriparatide) to the originator medicinal product containing teriparatide in patients with osteoporosis at high risk of fracture. The RMP (version 1.3) is updated accordingly

17.5. Interim results of imposed and non-imposed PASS submitted before the entry into force of the revised variation regulation

17.5.1. Alemtuzumab - LEMTRADA (CAP) - EMEA/H/C/003718/MEA 007.8

Applicant: Sanofi Belgium

PRAC Rapporteur: Anette Kirstine Stark

Scope: Fourth annual report for study OBS13434: a prospective, multicentre, observational PASS to evaluate the long term safety profile of Lemtrada (alemtuzumab) treatment in patients with relapsing forms of multiple sclerosis (MS) and to determine the incidence of adverse events of special interest (AESIs)

17.5.2. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 024.10

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report on adverse events and/or lack of efficacy, immunological data, follow-up growth disturbances in children and data on urinary hexose tetrasaccharide (Hex4) from the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children

17.5.3. Alglucosidase alfa - MYOZYME (CAP) - EMEA/H/C/000636/MEA 025.10

Applicant: Genzyme Europe BV

PRAC Rapporteur: Adrien Inoubli

Scope: Annual report on data on patients with renal or hepatic insufficiency from the Pompe registry: a global, observational and voluntary programme designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Pompe disease. The registry aims at detecting adverse events and/or lack of efficacy in patients, and at collecting immunological data, and follow-up growth disturbances in children

17.5.4. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/MEA 002.5

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: MAH's response to MEA 002.4 [third progress report and first interim report for study H9X-MC-B009: dulaglutide European modified prescription-event monitoring and network database study: a multi-database collaborative research programme of observational studies to monitor the utilisation and safety of dulaglutide in the EU] as per the request for supplementary information (RSI) adopted in December 2018

17.5.5. Empagliflozin - JARDIANCE (CAP) - EMEA/H/C/002677/MEA 005.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 005 request for supplementary for information (RSI) adopted in March 2018 and second interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

17.5.6. Empagliflozin, linagliptin - GLYXAMBI (CAP) - EMEA/H/C/003833/MEA 005.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 005 request for supplementary for information (RSI) adopted in March 2018 and second interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

17.5.7. Empagliflozin, metformin - SYNJARDY (CAP) - EMEA/H/C/003770/MEA 002.1

Applicant: Boehringer Ingelheim International GmbH

PRAC Rapporteur: Eva Segovia

Scope: MAH's response to MEA 002 request for supplementary for information (RSI) adopted in March 2018 and second interim report for an enhanced pharmacovigilance study 1245.146 to evaluate the risk of diabetic ketoacidosis (DKA) in patients treated with empagliflozin-containing product(s) as discussed with the FDA and requested in the conclusions of the referral procedure on sodium-glucose cotransporter-2 (SGLT2) inhibitors under Article 20 of Regulation (EC) No 726/2004 on diabetic ketoacidosis (DKA) (EMA/H/A-20/1419) finalised in 2016 [final clinical study report (CSR): Q4/2021]

17.5.8. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 002.2

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report from an established nationwide register (British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA)) for patients with rheumatological disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice

17.5.9. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 003.2

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report from an established nationwide register (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT)) for patients with rheumatological disorders treated with biologic agents, designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice

17.5.10. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 004.2

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report for study from ARTIS (Anti-Rheumatic Treatment in Sweden) register: a national prospective, observational, uncontrolled cohort study evaluating the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept

17.5.11. Etanercept - BENEPALI (CAP) - EMEA/H/C/004007/MEA 005.2

Applicant: Samsung Bioepis NL B.V.

PRAC Rapporteur: Eva Segovia

Scope: Third annual interim report for study from BADBIR (British Association of Dermatologists Biologic Interventions Register) register: a national prospective, observational, uncontrolled cohort study evaluating the risk of selected adverse events (AEs) in rheumatoid arthritis (RA), juvenile idiopathic arthritis, and other rheumatic disease patients treated with etanercept

17.5.12. Follitropin alfa - OVALEAP (CAP) - EMEA/H/C/002608/MEA 002.4

Applicant: Theramex Ireland Limited

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 002.3 [interim report for study XM17-WH-50005 (SOFIA): a non-interventional multinational prospective observational study to assess the safety of Ovaleap (follitropin alfa) compared to Gonal-F (follitropin alfa) in one treatment cycle with

respect to the incidence rates of ovarian hyperstimulation syndrome (OHSS) in infertile women undergoing superovulation for assisted reproductive technologies (ART)] as per the request for supplementary information (RSI) adopted in December 2018

17.5.13. Golimumab - SIMPONI (CAP) - EMEA/H/C/000992/MEA 033.2

Applicant: Janssen Biologics B.V.

PRAC Rapporteur: Ulla Wändel Liminga

Scope: Interim report for study MK-8259-050: an observational PASS for golimumab in treatment of poly-articular juvenile idiopathic arthritis (pJIA) using the German Biologics JIA registry (BiKeR)

17.5.14. Insulin detemir - LEVEMIR (CAP) - EMEA/H/C/000528/MEA 045.10

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Anette Kirstine Stark

Scope: Fifth annual progress report for diabetes pregnancy registry (NN304-4016): an international non-interventional prospective cohort study to evaluate the safety of treatment with insulin detemir in pregnant women with diabetes mellitus] as per the request for supplementary information (RSI) adopted in April 2018

17.5.15. Lonococog alfa - AFSTYLA (CAP) - EMEA/H/C/004075/MEA 002

Applicant: CSL Behring GmbH

PRAC Rapporteur: Daniela Philadelphia

Scope: Progress report for study CSL627_3001: a multicentre, open-label, phase 3 extension study which will investigate the safety and efficacy of recombinant factor VIII (rVIII)-single chain for prophylaxis and on-demand treatment of bleeding episodes in a total of at least 250 subjects with severe congenital haemophilia A

17.5.16. Nivolumab - OPDIVO (CAP) - EMEA/H/C/003985/MEA 008.5

Applicant: Bristol-Myers Squibb Pharma EEIG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: MAH's response to MEA 008.4 [second annual interim report for study CA209234 (listed as a category 3 study in the RMP): a PASS exploring the pattern of use, safety, and effectiveness of nivolumab in routine oncology practice [final clinical study report (CSR) due date: 31 December 2024] (from initial opinion/MA)] as per the request for supplementary information (RSI) adopted in December 2018

17.5.17. Octocog alfa - IBLIAS (CAP) - EMEA/H/C/004147/MEA 004

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Ninth annual European Haemophilia Safety Surveillance (EUHASS) report/first report for Iblis (octocog alfa) for study study 14149: evaluation of cases with adverse events

(AEs) of special interest in the EUHASS registry

17.5.18. Octocog alfa - HELIXATE NEXGEN (CAP) - EMEA/H/C/000276/MEA 085.7

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Ninth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149: evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry

17.5.19. Octocog alfa - KOGENATE BAYER (CAP) - EMEA/H/C/000275/MEA 086.7

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Ninth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149: evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry

17.5.20. Octocog alfa - KOVALTRY (CAP) - EMEA/H/C/003825/MEA 004.1

Applicant: Bayer AG

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Ninth annual European Haemophilia Safety Surveillance (EUHASS) report for study 14149: evaluation of cases with adverse events (AEs) of special interest in the EUHASS registry

17.5.21. Pegfilgrastim - NEULASTA (CAP) - EMEA/H/C/000420/MEA 060

Applicant: Amgen Europe B.V.

PRAC Rapporteur: Menno van der Elst

Scope: Sixth monthly summary report of medication error events reported with the on body injector in the EU market (from variation II/093/G)

17.5.22. Teduglutide - REVESTIVE (CAP) - EMEA/H/C/002345/ANX 003.4

Applicant: Shire Pharmaceuticals Ireland Limited

PRAC Rapporteur: Anette Kirstine Stark

Scope: Second biennial interim results for study TED-R-13-002: an international short bowel syndrome registry: a prospective, long-term observational cohort study of patients with short bowel syndrome

17.5.23. Ustekinumab - STELARA (CAP) - EMEA/H/C/000958/MEA 022.16

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Rhea Fitzgerald

Scope: Eighth annual report for study C0168Z03 (PSOLAR: PSOriasis Longitudinal Assessment and Registry): an international prospective cohort study/registry programme designed to collect data on psoriasis (PSO) patients that are eligible to receive systemic therapies, including generalised phototherapy and biologics

17.6. Others

17.6.1. Canagliflozin - INVOKANA (CAP) - EMEA/H/C/002649/MEA 014.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Martin Huber

Scope: MAH's response to MEA 014 [protocol for meta-analysis of amputation events from clinical trials DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy), as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in December 2018

17.6.2. Canagliflozin, metformin - VOKANAMET (CAP) - EMEA/H/C/002656/MEA 013.1

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Menno van der Elst

Scope: MAH's response to MEA 013 [protocol for meta-analysis of amputation events from clinical trials DIA3008 (CANVAS: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of JNJ-28431754 (canagliflozin) on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus (T2DM)), DIA4003 (CANVAS-R: a randomized, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on renal endpoints in adult subjects with T2DM), and DNE3001 (CREDENCE: a randomised, double-blind, event-driven, placebo-controlled, multicentre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and diabetic nephropathy), as per the outcome of the referral procedure under Article 20 of Regulation (EC) No 726/2004 on lower limb amputation in relation to the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors completed in February 2017 (EMA/H/A-20/1442)] as per the request for supplementary information (RSI) adopted in December 2018

17.6.3. Eribulin - HALAVEN (CAP) - EMEA/H/C/002084/MEA 022

Applicant: Eisai GmbH

PRAC Rapporteur: Annika Folin

Scope: Statistical analysis plan for study E7389-M044-504: an observational post-authorisation, single-arm, prospective, multicentre cohort study to investigate the

frequency of and time to resolution of eribulin-induced or aggravated peripheral neuropathy (PN) in patients with locally advanced or metastatic breast cancer in a real-life setting (from variation II/33)

17.6.4. Fingolimod - GILENYA (CAP) - EMEA/H/C/002202/MEA 038

Applicant: Novartis Europharm Limited

PRAC Rapporteur: Ghania Chamouni

Scope: Amendment to the previously agreed protocol for study D2311: a double-blind, randomized, multicentre, active controlled study evaluating efficacy and safety of fingolimod administered orally once daily versus interferon β -1a once weekly in paediatric patients with multiple sclerosis (MS) aged 10 to <18 years old (from X/44/G)

17.6.5. Infliximab - INFLECTRA (CAP) - EMEA/H/C/002778/MEA 016

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Kimmo Jaakkola

Scope: Pooled analysis of non-interventional registry data from a minimum of 3,100 patients aiming at evaluating the risk of tuberculosis and serious infections (in fulfilment of MEA 016). The analysis includes pooled data from studies: 1) Korean post-marketing surveillance (PMS) observational study; 2) study CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra/Remsuma (infliximab) in patients with rheumatoid arthritis (EU); 3) registry CT P13 4.3: an observational, prospective cohort study to evaluate the safety and efficacy of Inflectra/Remsuma (infliximab) in patients with Crohn's disease (CD) or ulcerative colitis (UC) (EU and Korea); 4) registry CT P13 4.4: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra/Remsuma (infliximab) in patients with ankylosing spondylitis (EU); 5) British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA): a longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK); 6) Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): long-term observation of treatment with biologics in rheumatoid arthritis (Germany); 7) PERSIST: a prospective observational cohort study to assess persistence of Inflectra/Remsuma (infliximab) in patients with rheumatoid diseases who are either naive to biologics or switched from stable infliximab originator's containing product; 8) post-marketing observational cohort study of patients with inflammatory bowel disease (IBD) treated with Inflectra/Remsuma (infliximab) in usual clinical practice (CONNECT-IBD)

17.6.6. Infliximab - REMSIMA (CAP) - EMEA/H/C/002576/MEA 016

Applicant: Celltrion Healthcare Hungary Kft.

PRAC Rapporteur: Kimmo Jaakkola

Scope: Pooled analysis of non-interventional registry data from a minimum of 3,100 patients aiming at evaluating the risk of tuberculosis and serious infections (in fulfilment of MEA 016). The analysis includes pooled data from studies: 1) Korean post-marketing surveillance (PMS) observational study; 2) study CT-P13 4.2: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra/Remsuma (infliximab) in patients with rheumatoid arthritis (EU); 3) registry CT P13 4.3: an observational, prospective cohort

study to evaluate the safety and efficacy of Inflectra/Remsima (infliximab) in patients with Crohn's disease (CD) or ulcerative colitis (UC) (EU and Korea); 4) registry CT P13 4.4: an observational, prospective cohort study to evaluate safety and efficacy of Inflectra/Remsima (infliximab) in patients with ankylosing spondylitis (EU); 5) British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA): a longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK); 6) Rheumatoide Arthritis: Beobachtung der Biologika-Therapie (RABBIT): long-term observation of treatment with biologics in rheumatoid arthritis (Germany); 7) PERSIST: a prospective observational cohort study to assess persistence of Inflectra/Remsima (infliximab) in patients with rheumatoid diseases who are either naive to biologics or switched from stable infliximab originator's containing product; 8) post-marketing observational cohort study of patients with inflammatory bowel disease (IBD) treated with Inflectra/Remsima (infliximab) in usual clinical practice (CONNECT-IBD)

17.6.7. Lopinavir, ritonavir - KALETRA (CAP) - EMEA/H/C/000368/LEG 121.1

Applicant: AbbVie Deutschland GmbH & Co. KG

PRAC Rapporteur: Adrien Inoubli

Scope: Annual safety review in children aged from 14 days to 2 years as regards to chronic exposure to propylene glycol and ethanol and toxicity, medication errors and lack of efficacy/resistance in relation to potentially suboptimal pharmacokinetic (PK) parameters

17.7. New Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

17.8. Ongoing Scientific Advice

None

17.9. Final Scientific Advice (Reports and Scientific Advice letters)

None

18. Annex I – Renewals of the marketing authorisation, conditional renewals and annual reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

18.1. Annual reassessments of the marketing authorisation

18.1.1. Afamelanotide - SCENESSE (CAP) - EMEA/H/C/002548/S/0023 (without RMP)

Applicant: Clinuvel Europe Limited

PRAC Rapporteur: Martin Huber

Scope: Annual reassessment of the marketing authorisation

18.1.2. Cholic acid - KOLBAM (CAP) - EMEA/H/C/002081/S/0029 (without RMP)

Applicant: Retrophin Europe Ltd

PRAC Rapporteur: Agni Kapou

Scope: Annual reassessment of the marketing authorisation

18.1.3. Cholic acid - ORPHACOL (CAP) - EMEA/H/C/001250/S/0026 (without RMP)

Applicant: Laboratoires CTRS

PRAC Rapporteur: Sophia Trantza

Scope: Annual reassessment of the marketing authorisation

18.1.4. Mecasermin - INCRELEX (CAP) - EMEA/H/C/000704/S/0055 (with RMP)

Applicant: Ipsen Pharma

PRAC Rapporteur: Kirsti Villikka

Scope: Annual reassessment of the marketing authorisation

18.1.5. Susoctocog alfa - OBIZUR (CAP) - EMEA/H/C/002792/S/0023 (without RMP)

Applicant: Baxalta Innovations GmbH

PRAC Rapporteur: Brigitte Keller-Stanislawski

Scope: Annual reassessment of the marketing authorisation

18.1.6. Tafamidis - VYNDAQEL (CAP) - EMEA/H/C/002294/S/0047 (without RMP)

Applicant: Pfizer Europe MA EEIG

PRAC Rapporteur: Ghania Chamouni

Scope: Annual reassessment of the marketing authorisation

18.2. Conditional renewals of the marketing authorisation

18.2.1. Ataluren - TRANSLARNA (CAP) - EMEA/H/C/002720/R/0051 (with RMP)

Applicant: PTC Therapeutics International Limited

PRAC Rapporteur: Liana Gross-Martirosyan

Scope: Conditional renewal of the marketing authorisation

18.2.2. Avelumab - BAVENCIO (CAP) - EMEA/H/C/004338/R/0008 (without RMP)

Applicant: Merck Europe B.V.

PRAC Rapporteur: Anette Kirstine Stark

Scope: Conditional renewal of the marketing authorisation

18.3. Renewals of the marketing authorisation

18.3.1. Busulfan - BUSULFAN FRESENIUS KABI (CAP) - EMEA/H/C/002806/R/0010 (with RMP)

Applicant: Fresenius Kabi Deutschland GmbH

PRAC Rapporteur: Eva Segovia

Scope: 5-year renewal of the marketing authorisation

18.3.2. Dolutegravir, abacavir, lamivudine - TRIUMEQ (CAP) - EMEA/H/C/002754/R/0063 (with RMP)

Applicant: ViiV Healthcare B.V.

PRAC Rapporteur: Martin Huber

Scope: 5-year renewal of the marketing authorisation

18.3.3. Dulaglutide - TRULICITY (CAP) - EMEA/H/C/002825/R/0036 (with RMP)

Applicant: Eli Lilly Nederland B.V.

PRAC Rapporteur: Amelia Cupelli

Scope: 5-year renewal of the marketing authorisation

18.3.4. Filgrastim - ACCOFIL (CAP) - EMEA/H/C/003956/R/0026 (without RMP)

Applicant: Accord Healthcare S.L.U.

PRAC Rapporteur: Kirsti Villikka

Scope: 5-year renewal of the marketing authorisation

18.3.5. Ibrutinib - IMBRUVICA (CAP) - EMEA/H/C/003791/R/0049 (with RMP)

Applicant: Janssen-Cilag International NV

PRAC Rapporteur: Nikica Mirošević Skvrce

Scope: 5-year renewal of the marketing authorisation

18.3.6. Insulin degludec, liraglutide - XULTOPHY (CAP) - EMEA/H/C/002647/R/0028 (with RMP)

Applicant: Novo Nordisk A/S

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

18.3.7. Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) - ADJUPANRIX (CAP) - EMEA/H/C/001206/R/0062 (with RMP)

Applicant: GlaxoSmithkline Biologicals SA

PRAC Rapporteur: Menno van der Elst

Scope: 5-year renewal of the marketing authorisation

19. Annex II - List of participants

including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 08 – 11 April 2019 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Sabine Straus	Chair	The Netherlands	No interests declared	Full involvement
Jan Neuhauser	Member	Austria	No interests declared	Full involvement
Jean-Michel Dogné	Member	Belgium	No interests declared	Full involvement
Laurence de Fays	Alternate	Belgium	No interests declared	Full involvement
Željana Margan Koletić	Alternate	Croatia	No interests declared	Full involvement
Eva Jirsovà	Member	Czech Republic	No interests declared	Full involvement
Anette Kirstine Stark	Member	Denmark	No interests declared	Full involvement
Maia Uusküla	Member	Estonia	No interests declared	Full involvement
Kirsti Villikka	Member	Finland	No interests declared	Full involvement
Kimmo Jaakkola	Alternate	Finland	No interests declared	Full involvement
Ghania Chamouni	Member	France	No participation in discussion, final deliberations and voting on:	16.1.11. Eluxadoline - TRUBERZI (CAP)
Adrien Inoubli	Alternate	France	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Martin Huber	Member (Vice-Chair)	Germany	No interests declared	Full involvement
Brigitte Keller-Stanislowski	Alternate	Germany	No interests declared	Full involvement
Agni Kapou - via telephone*	Member	Greece	No interests declared	Full involvement
Sophia Trantza	Alternate	Greece	No restrictions applicable to this meeting	Full involvement
Julia Pallos	Member	Hungary	No interests declared	Full involvement
Rhea Fitzgerald	Member	Ireland	No restrictions applicable to this meeting	Full involvement
Ronan Grimes	Alternate	Ireland	No interests declared	Full involvement
Amelia Cupelli	Member	Italy	No interests declared	Full involvement
Zane Neikena	Member	Latvia	No interests declared	Full involvement
Rugile Pilvinienė	Member	Lithuania	No interests declared	Full involvement
Ruta Kerpauskiene	Alternate	Lithuania	No interests declared	Full involvement
Marcel Bruch	Member	Luxembourg	No interests declared	Full involvement
Benjamin Micallef	Alternate	Malta	No interests declared	Full involvement
Menno van der Elst	Member	Netherlands	No interests declared	Full involvement
Liana Gross-Martirosyan	Alternate	Netherlands	No interests declared	Full involvement
David Olsen	Member	Norway	No participation in discussion, final deliberations and voting on:	4.3.2. Direct-acting oral anticoagulants (DOACs): apixaban - ELIQUIS (CAP) - ; dabigatran etexilate - PRADAXA (CAP); edoxaban - LIXIANA (CAP), ROTEAS (CAP); rivaroxaban - XARELTO (CAP); 4.3.7. Sorafenib - NEXAVAR (CAP); 16.1.27. Riociguat - ADEMPAS (CAP)

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				6.1.12. Rivaroxaban - XARELTO (CAP); 17.5.17. Octocog alfa - IBLIAS (CAP) 17.5.18. Octocog alfa - HELIXATE NEXGEN (CAP) 17.5.19. Octocog alfa - KOGENATE BAYER (CAP) 17.5.20. Octocog alfa - KOVALTRY (CAP)
Karen Pernille Harg	Alternate	Norway	No interests declared	Full involvement
Adam Przybylkowski	Member	Poland	No interests declared	Full involvement
Ana Diniz Martins	Member	Portugal	No interests declared	Full involvement
Marcia Silva - via telephone*	Alternate	Portugal	No interests declared	Full involvement
Roxana Stefania Stroe	Member	Romania	No interests declared	Full involvement
Michal Radik	Member	Slovakia	No restrictions applicable to this meeting	Full involvement
Gabriela Jazbec	Member	Slovenia	No interests declared	Full involvement
Eva Segovia	Member	Spain	No interests declared	Full involvement
Maria del Pilar Rayon	Alternate	Spain	No interests declared	Full involvement
Ulla Wändel Liminga	Member	Sweden	No interests declared	Full involvement
Annika Folin	Alternate	Sweden	No interests declared	Full involvement
Julie Williams	Member	United Kingdom	No interests declared	Full involvement
Patrick Batty	Alternate	United Kingdom	No interests declared	Full involvement
Birgitta Grundmark	Member	Independent scientific expert	No interests declared	Full involvement
Daniel Morales	Member	Independent scientific expert	No interests declared	Full involvement
Hedvig Nordeng	Member	Independent scientific expert	No interests declared	Full involvement
Antoine Pariente	Member	Independent scientific expert	No restrictions applicable to	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
			this meeting	
Livia Puljak	Member	Independent scientific expert	No interests declared	Full involvement
Stefan Weiler	Member	Independent scientific expert	No restrictions applicable to this meeting	Full involvement
Raymond Anderson	Member	Healthcare Professionals' Representative	No interests declared	Full involvement
Cathalijne van Doorne	Member	Patients' Organisation Representative	No interests declared	Full involvement
Virginie Hivert	Alternate	Patients' Organisation Representative	No restrictions applicable to this meeting	Full involvement
Martin Zahle Larsen	Expert - in person*	Denmark	No interests declared	Full involvement
Päivi Susanna Worsøe	Expert - in person*	Denmark	No participation in discussion, final deliberations and voting on:	Full involvement
Henning Brohmann	Expert - via telephone*	Germany	No interests declared	Full involvement
Anne Kleinau	Expert - via telephone*	Germany	No interests declared	Full involvement
Jens Rotthauwe	Expert - via telephone*	Germany	No interests declared	Full involvement
Wiebke Seemann	Expert - via telephone*	Germany	No interests declared	Full involvement
Valerie Strassmann	Expert - in person*	Germany	No interests declared	Full involvement
Kate Browne	Expert - via telephone*	Ireland	No interests declared	Full involvement
Emma Lawless	Expert - via telephone*	Ireland	No interests declared	Full involvement
Quirine Fillekes	Expert - in person*	Netherlands	No interests declared	Full involvement
Pim Luijsterburg	Expert - via telephone*	Netherlands	No interests declared	Full involvement
Almudena López-Fando	Expert - in person*	Spain	No interests declared	Full involvement
Dolores Montero Corominas	Expert - via telephone*	Spain	No interests declared	Full involvement
Charlotte Backman	Expert - in person*	Sweden	No interests declared	Full involvement
Karin Bolin	Expert - via telephone*	Sweden	No interests declared	Full involvement
Sofia Bosdotter Enroth	Expert - via telephone*	Sweden	No interests declared	Full involvement

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Anna Vikerfors	Expert - via telephone*	Sweden	No interests declared	Full involvement
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in

20. Annex III - List of acronyms and abbreviations

For a list of acronyms and abbreviations used in the PRAC minutes, see:

[Home>Committees>PRAC>Agendas, minutes and highlights](#)

21. Explanatory notes

The Notes give a brief explanation of relevant minute's items and should be read in conjunction with the minutes.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures

(Items 2 and 3 of the PRAC minutes)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation

(Item 4 of the PRAC minutes)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.

The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)

(Item 5 of the PRAC minutes)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)

(Item 6 of the PRAC minutes)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.

PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)

(Item 7 of the PRAC minutes)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections

(Item 9 of the PRAC minutes)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website:

<http://www.ema.europa.eu/ema/>